women & children's health research institute

Research Day Abstract booklet

#WCHRIRD2018

Acknowledgements

Thank you

The amazing research on display today, and all of the other services and supports that WCHRI offers, wouldn't be possible without the continued partnership of the University of Alberta, Alberta Health Services, the Stollery Children's Hospital Foundation and the supporters of the Lois Hole Hospital for Women.

Through the support of our partners, we are able to gather some of the most brilliant minds in research together to collaborate and share ideas that will make the future of both women and children brighter.

List of presenters

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DISCLAIMER:
While the abstracts have been slightly modified for consistency, each abstract has been predominantly printed exactly as originally submitted.

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Abstract #: 1
Presenter: Sonia Rawat
Supervisor: Gary D. Lopaschuk
Title: Cardiac hypertrophy in neonates with congenital heart disease delays maturational increase in fatty acid oxidation by modifying myocardial acetylatio
Authors: Arata Fukushima, Liyan Zhang, Alda Huqi, Victoria H. Lam, Tariq Altamimi, Cory S. Wagg, Khushmol K. Dhaliwal, Lisa K. Hornberger, Paul F. Kantor, Ivan M. Rebeyka
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Congenital heart disease (CHD) affects more than 1% of newborns, causing atypical functioning and blood flow in the heart, and the possible development of hypertrophy. Cardiac hypertrophy delays the normal maturational process by reducing fatty acid oxidation, resulting in a decrease in energetic capacity and an increased susceptibility to ischemic injury during corrective surgery for CHDs. Protein lysine acetylation has emerged as a novel posttranslational modification that enhances fatty acid oxidation. However, the importance of lysine acetylation in human newborn heart metabolism and hypertrophy has yet to be elucidated. Therefore, we investigated how changes in lysine acetylation contribute to metabolic changes in hypertrophied neonatal hearts following maturation.

Methods: Human myocardial samples were collected from infants undergoing corrective heart surgery and stratified in two age groups (21-100 days and 101-200 days) and further stratified based on the presence or absence of hypertrophy assessed by echocardiography. Rabbits with hypertrophy induced by an aortocaval shunt were also used for *ex vivo* isolated working heart perfusions to determine the flux through metabolic pathways. All heart tissues were processed for acetylation status using immunoprecipitation and for enzyme activities. Additionally, gene knockdown of *Gcn5l1* in neonatal rat cardiomyocytes (H9c2 cells) with phenylephrine-induced hypertrophy highlighted the importance of acetylation in the newborn setting.

Results: The overall acetylation of myocardial proteins was significantly increased with age in non-hypertrophied human hearts, whereas the age-dependent increase was blunted in hypertrophied hearts. These changes in the acetylation also occurred in key mitochondrial proteins. In particular, an age dependent hyperacetylation of fatty acid oxidation enzymes long chain acyl CoA dehydrogenase (LCAD) andβ-hydroxyacyl CoA dehydrogenase (β-HAD) was positively correlated with their enzymatic activity (β-HAD R^2=0.54; LCAD R^2=0.50) only in non-hypertrophied hearts. In line with this, a reduced acetylation of LCAD and β-HAD was also observed in hypertrophied hearts from 21-day old rabbits subjected to aortocaval shunt, in which a decrease in fatty acid oxidation rates occurred. In addition, a decrease in the acetylation of mitochondrial acetyltransferase GCN5L1 was observed in the hypertrophied hearts and silencing *Gcn5l1* reduced acetylation of LCAD and β-HAD, as well as fatty acid β-oxidation rates *in vitro*.

Conclusions: Cardiac hypertrophy in CHD patients prevents the normal increase in myocardial acetylation following birth, resulting in a delayed maturation of fatty acid oxidation.

Funded By: WCHRI Innovation Grant; CIHR

Abstract #: 2
Presenter: Deliwe P Ngwezi
Supervisor: Lisa K Hornberger
Title: Neighborhood socio-economic status and congenital heart disease in urban Alberta
Authors: Deliwe P Ngwezi, Lisa K Hornberger, Deborah Fruitman, Alvaro Osornio-Vargas
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: The etiology of congenital heart disease (CHD), which affects 1% of live births worldwide, is unknown for many affected patients. Previous studies have demonstrated associations between individual maternal socioeconomic status (SES) and CHD; whereas, the contribution of neighborhood SES on CHD development has been inconclusive. We had previously found independent positive associations between CHD occurrence and high developmental toxicant (DT) exposures in urban and rural regions of Alberta. In this study we sought to: 1) explore the association between neighborhood SES and CHD 2) map SES and CHD cases in urban regions and 3) map the collocation of high DT exposure and low SES and CHD in urban regions.

Methods: We identified all children born with CHD in Alberta between 2004 and 2011 from provincial echocardiographic databases. We used Chan's SES index which was constructed at dissemination area (DA) level from 22 variables obtained from Census Canada 2006. The index was assigned to the postal codes belonging to respective DAs. We categorized the index into tertiles and assigned CHD cases to the tertiles : tertile (1) reflecting the lowest and tertile (3) the highest SES which was the reference. We conducted Poisson regression models adjusted for all industrial DTs released to air and criteria pollutants related variables (NO_2, $PM_{2.5}$). Centroids of the postal codes of low SES locations, CHD cases and exposed to the highest DT emissions were displayed using ESRI ArcGIS 10.4 software.

Results: There was a significant increased risk ratio of urban CHD in the lowest SES tertile [RR = 1.1, CI: 1.0, 1.3] compared to the highest SES tertile. Mapping revealed that 4% (692/18,009) of postal codes collocated with low SES and CHD. The proportion of CHD cases in those postal codes was 38% (743/1,967). Furthermore, collocation of high DT exposures, low SES and CHD, occurred in only 7% (174/2,447) postal codes (mostly in Edmonton) and these had 10% (189/1,967) of CHD cases. The risk ratio for combined DT exposures and low SES was [RR =1.96, CI: 1.53, 2.51] compared to lowest DT exposures and high SES regions.

Conclusions: Low neighborhood SES was associated with an increased CHD risk in urban Alberta. The risk was independent of DT exposures shown in our previous analysis. The findings from collocation mapping, suggest the presence of a localized environmental injustice in urban, Alberta.

Funded By: WCHRI Innovation Grant; Graduate Studentship; CHIR; Hamilton Naki Scholarship (South Africa)

Abstract #: 3
Presenter: Golam M. Uddin
Supervisor: Gary D. Lopaschuk
Title: Reduced cardiac branched chain amino acid (BCAA) catabolism is associated with impaired insulin signalling in the human failing heart
Authors: Golam M Uddin, Liyan Zhang, Arata Fukushima, Tariq Altamimi, Saumya Shah, Gavin Y. Oudit, Gary D. Lopaschuk
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

INTRODUCTION: Alterations in cardiac energy metabolism contribute to the development and severity of heart failure. Interestingly, anaccumulation of cardiac BCAA is a potentially important signature of metabolic reprogramming and insulin resistance in the failing heart. However, it is not known whether cardiac insulin signalling is impaired due to altered BCAA catabolism in the failing heart. Here, we aim to determine if impaired BCAA catabolism in dilated cardiomyopathy (DCM) contributes to cardiac insulin resistance.

METHOD: Male and female patients with DCM (n=6) aged 22-66 years old were recruited with informed consent from University of Alberta hospital. Left ventricular biopsies were obtained at the time of transplantation. Control biopsies were obtained from non-transplanted donor hearts without heart disease history.

RESULTS: Echocardiographic data showed a reduction in ejection fraction and an enhanced formation of cardiac fibrosis in DCM patients when compared to the control patients. Hearts from DCM patients showed a blunted insulin signalling pathway, as indicated by an increase in p-IRS1ser636/639 and its upstream modulator p-p70S6K, but a decrease in its downstream modulators p- AKT ser473 and in p-GSK3β ser9. Levels of cardiac BCAAs were significantly elevated in DCM hearts, concomitant with a decrease in the expression of the BCAA oxidative enzymes BCAA transferase (0.4±0.09 vs 1±0.2, n=6, $p<0.05$) and protein phosphatase 2Cm (0.6±0.19 vs 1±0.1, n=6, $p<0.05$). A decreased expression of KLF15, an upstream regulator of the BCAA oxidation, was observed in DCM hearts with an increased p-TAK1 thr187, p-p38 MAPK, which are the negative-regulators of KLF15. In addition, mTOR signalling was activated in DCM hearts with the upregulation of phosphorylated mTOR ser2448 (2.3±0.5 vs 1±0.2, n=6, $p<0.05$).

CONCLUSION: Patient with DCM showed myocardial mTOR activation leading to IRS1 phosphorylation and impaired insulin signalling, which may be a result of decreased myocardial BCAA catabolism.

Funded By:

Abstract #: 4
Presenter: Qutuba Karwi
Supervisor: Gary Lopaschuk
Title: Antagonizing glucagon signalling following myocardial infarction enhances cardiac function and insulin signalling
Authors: Qutuba Karwi, Liyan Zhang, Cory Wagg, Wang Wang, John Ussher, Gavin Oudit, Gary Lopaschuk
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Glucagon's action on cardiac glucose and lipid homeostasis counteract that of insulin's action. In heart failure, the myocardium becomes insulin resistant which influences cardiac metabolism and function. We sought to determine if antagonising myocardial glucagon action, using a human monoclonal antibody (mAb A) against the G coupled glucagon receptor, enhances insulin sensitivity and improves cardiac energy metabolism and function post myocardial infarction (MI).

Methods

Male C57BL/6 mice were subjected to either sham surgery or a permanent left anterior descending coronary artery ligation surgery to induce myocardial infarction. A week after the induction of myocardial infarction, mice were randomised to receive either saline or mAb A treatment (4 mg/kg/week) for 3 weeks. Cardiac function and hypertrophy were monitored using echocardiography. Hearts were collected and perfused in an isolating working heart model to access cardiac energy metabolism at the end of the treatment protocol. Myocardial biopsies were isolated at the end of the perfusion for molecular biochemistry.

Results

mAb A treatment resulted in an improved ejection fraction (30.7 ± 1.8 (n=31) to 39.7 ± 2.3 (n=28) in vehicle vs mAb A treated mice) and limited adverse remodelling (i.e. decreased dilation and cardiac hypertrophy). mAb A-mediated cardioprotection post-MI was associated with an activation of the IRS-1/Akt/GSK-3β pathway and increased GLUT4 expression. Enhanced insulin signalling along with a reduction in pyruvate dehydrogenase (PDH) phosphorylation resulted in a marked increase in insulin-stimulated glucose oxidation rates in the post-MI hearts. Furthermore, glucose oxidation contribution toward tricarboxylic acid (TCA) cycle acetyl CoA production, measured in isolated working hearts, was also significantly increased. Intriguingly, there was a significant reduction in cardiac ketone oxidation rates in the post-MI hearts which were further decreased by mAb A treatment. The decreased cardiac remodelling by mAb A treatment was associated with inhibition of cardiac mTOR/P70S6K signalling compared to the vehicle-treated post-MI mice.

Conclusions

Antagonising the cardiac glucagon receptor with mAb A improves cardiac contractility and prevents adverse remodelling post-MI. mAb A-induced cardioprotection is associated with improving insulin sensitivity and a selective enhancement of glucose oxidation contribution to TCA acetyl CoA production post-MI. Antagonizing glucagon action represents a novel and effective intervention to alleviate cardiac dysfunction and adverse remodelling post-MI.

Funded By: REMD Biotherapeutics

Abstract #: 5
Presenter: Jacob Chacko
Supervisor: Jennifer Conway
Title: Readmission to the pediatric cardiac intensive care unit in pediatric patients with durable ventricular assist Devices
Authors: Jacob Chacko, Tara Pidborochynski, Holger Buchholz, Paula Holinski, Vijay Anand, Darren Freed, Jennifer Conway
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction:

Pediatric patients implanted with durable ventricular assist devices (VADs) are managed in the pediatric intensive care unit (PICU) after implant, but are eligible to be transferred to the ward once stable. Currently there is no literature regarding the impact of readmission to the PICU in this patient population. Therefore, the primary aim of this study was to characterize readmissions to the PICU, identifying possible risk factors for readmission and determining whether readmission is associated with increased mortality.

Methods:

This was a retrospective study of all patients <21 years of age at the Stollery Children's Hospital who had a durable VAD implanted between 2005-16.

Results:

There were 44 patients who underwent durable VAD implantation during the study period. The median age of implant was 3.7 yrs (IQR 0.64 – 8.9), 57% were males and the most common etiology was cardiomyopathy (53%). The median time of VAD support was 110 days (IQR 42.3 – 212.3) with the median index ICU stay being 34 days (IQR 19.8 – 81). Thirty patients (68%) were discharged to the ward with 18 (60%) having at least 1 readmission with 46 total readmissions. The median time to first readmission was 18 days (IQR 14.8 – 110.3). The median number of readmissions per patient was 2 (IQR 1 – 3) with a readmission rate of 0.71/ per 100 patient days of VAD support. The most common cause of readmission was pump thrombosis (34%) followed by neurologic dysfunction (23%). There were no statistically significant pre or post implant factors identified to be associated with readmission. Readmission was also not associated with mortality (p=0.6). However, there was a statistically significant association between never being discharged from the index ICU stay and death on device (p=.001), with the majority of all deaths (7/8) occurring before the index discharge.

Conclusion:

Readmissions to the PICU occurred in over 50% of patients on durable VAD support with first readmission occurring on average within the month post discharge. While, there were no clear factors identified associated with readmission, discharge from index ICU stay was associated with decreased mortality.

Funded By: WCHRI Summer Studentship; Alberta Innovates

Abstract #: 6
Presenter: Simran Pherwani
Supervisor: Gary Lopaschuk
Title: Enhanced branched chain amino acid catabolism improves contractile function in the failing heart
Authors: Simran Pherwani , Golam Uddin, Liyan Zhang, Arata Fukushima, Cory Wagg, Tariq Altamimi, Jaimmi Boisvenue, John Ussher, Jason Dyck, Gary Lopaschuk
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Alterations in cardiac energy metabolism can have a profound impact on the establishment and severity of cardiac pathologies including heart failure. In the failing heart, branched chain amino acids (BCAAs) are markedly elevated, possibly due to impaired cardiac BCAA oxidation, which can lead to insulin-resistance and further progression of heart failure. Key enzymes in the BCAA catabolic pathway, such as branched-chain α-keto acid dehydrogenase (BCKDH), are controlled by phosphorylation via kinases such as BCKDH kinase (BCKDK), rendering them inactive. We hypothesized that increasing BCAA catabolism by pharmacologically inhibiting BCKDK would decrease BCAAs and improve the pathophysiology of heart failure.

Methods

To test this, adult mice were subjected to either a transverse aortic constriction to induce pressure overload hypertrophy, or to sham surgery, following which they were treated with the BCKDK inhibitor (BT2) or vehicle between 1-week and 4-weeks post surgery. Echocardiography data were obtained after 4 weeks to assess cardiac function, following which hearts were subjected to isolated working heart perfusions.

Results

There was a significant decrease in cardiac function (45.8±3.1 vs 54.3±3.8% ejection fraction) in TAC mice compared to sham. The BT2 injection significantly improved cardiac function in both sham and TAC mice (63.0±1.8 and 56.9±3.8% ejection fraction respectively). In a parallel series of isolated working heart perfusions from control mice, BT2 was shown to acutely stimulate BCAA oxidation. Furthermore, a significant decrease in BCKDH phosphorylation due to BT2 injection supports an increase in BCAA catabolism. Additionally, BCKDK expression was significantly decreased in the BCKDK inhibitor treated groups.

Conclusion

We conclude that BCKDK inhibition by BT2 results in an improvement of BCAA oxidation and cardiac function in the failing heart. Improving BCAA catabolism may provide a potential future therapeutic approach to treat heart failure.

Funded By: Motyl Endowment Cardiac Sciences Summer Studentship Award

Abstract #: 7
Presenter: Rachel Skow
Supervisor: Margie Davenport
Title: The effects of prenatal exercise on fetal heart rate, umbilical and uterine blood flow: a systematic review and meta-analysis.
Authors: Rachel Skow, Margie Davenport, Michelle Mottola, Greg Davies, Veronica Poitras, Casey Gray, Nick Barrowman, Victoria Meah, Linda Slater, Kristi Adamo, Ruben Barakat, Stephanie Ruchat
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Objective: To perform a systematic review and meta- analysis examining the influence of acute and chronic prenatal exercise on fetal heart rate (FHR) and umbilical and uterine blood flow metrics.

Design: Systematic review with random-effects meta- analysis and meta-regression.

Data sources: Online databases were searched up to 6 January 2017.

Study eligibility criteria: Studies of all designs were included (except case studies) if published in English, Spanish or French, and contained information on the population (pregnant women without contraindication to exercise), intervention (subjective or objective measures of frequency, intensity, duration, volume or type of exercise), comparator (no exercise or different frequency, intensity, duration, volume and type of exercise) and outcomes (FHR, beats per minute (bpm); uterine and umbilical blood flow metrics (systolic:diastolic (S/D) ratio; Pulsatility Index (PI); Resistance Index (RI); blood flow, mL/min; and blood velocity, cm/s)).

Results: 'Very low' to 'moderate' quality evidence from 91 unique studies (n=4641 women) were included. Overall, FHR increased during (mean difference (MD)=6.35bpm; 95% CI 2.30 to 10.41, I2=95%, p=0.002) and following acute exercise (MD=4.05; 95% CI 2.98 to 5.12, I2=83%, p<0.00001). The incidence of fetal bradycardia was low at rest and unchanged with acute exercise. There were no significant changes in umbilical or uterine S/D, PI, RI, blood flow or blood velocity during or following acute exercise sessions. Chronic exercise decreased resting FHR and the umbilical artery S/D, PI and RI at rest.

Conclusion: Acute and chronic prenatal exercise do not adversely impact FHR or uteroplacental blood flow metrics.

Funded By: CIHR, CSEP

Abstract #: 8
Presenter: Sana Amjad
Supervisor: Maria Ospina
Title: Area of Residence, Socioeconomic Status and the Risk of Adverse Maternal and Birth Outcomes in Adolescent Pregnancies
Authors: Sana Amjad, Alvaro Osornio Vargas, Sujata Chandra, Don Voaklander, Maria-Beatriz Ospina
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Adolescent pregnancy is an important public health issue in Canada. About 40,000 Canadian adolescents become pregnant every year. Poor outcomes in adolescent pregnancy are likely associated with social determinants of health such as low socioeconomic status (SES) and rural residence. Few studies have explored the combined effect of these factors on pregnancy outcomes of adolescent mothers. Using population-based data from Alberta, this study investigated the joint effect of maternal area of residence and SES on adolescent pregnancy outcomes.

Methods: The study population consisted of all pregnant women aged 15-19 years who gave singleton live births between April 1, 2010, to March 31, 2015, in Alberta. We used the Alberta Perinatal Health Program, and the Pampalon Material Deprivation Index Dataset to obtain information on maternal residence, SES and obstetric and perinatal outcomes. Mothers were categorized into four groups based on their SES and residence status: rural/high SES; rural/low SES; urban/high SES; and urban/low SES. Data were analyzed with descriptive statistics and logistic regression models using urban/high SES group as the reference category.

Results: There were 9,606 births to adolescent mothers during the study period. Overall, 30% of the mothers were in the urban/high SES group; 27% in the urban/low SES group; 7% in the rural/high SES group and 36% had rural residence and low SES. Rural residents with low SES have increased odds of postpartum hemorrhage (Odds Ratio [OR]:1.57; 95% confidence interval [CI]: 1.41-1.74); operative vaginal delivery (OR: 1.37; 95% CI: 1.18-1.60), cesarean section (OR:1.39; 95% CI: 1.19-1.62) and preterm birth (OR: 1.48; 95% CI:1.17-1.87).

Conclusion: Rural adolescent mothers with low SES have an increased risk of adverse pregnancy outcomes. Study results can help to inform perinatal programs for adolescent mothers in Alberta and elsewhere. Social predictors of adolescent pregnancy outcomes need further exploration to highlight potential areas of intervention.

Abstract #: 9
Presenter: Bijaya Pokharel
Supervisor: Kathy Hegadoren
Title: Factors influencing silencing about intimate partner violence: An ecological analysis
Authors: Bijaya Pokharel, Kathy Hegadoren, Elisavet Papathanasoglou
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Globally, 30% of the female population experience sexual or physical Intimate Partner Violence (IPV); whereas, those data may underestimate the extent of the problem due to the issue of silencing associated with IPV. Silencing puts affected women at higher risk for acute and chronic health impacts. In Canada, between 2001 and 2011, murder committed by spouses accounted for the highest proportion of homicide murders; 97% of the victims were female. A large number of studies about factors influencing silencing has been published. An ecological synthesis of these studies can provide a better understanding of the multiple factors at play. Thus, we aimed to use an ecological model to synthesize the existing literature on the factors influencing the silencing of women about IPV.

Methods

We used an integrative review design. Seven databases (PubMed, CINAHL, Scopus, Web of Science, Gender Studies, Sociological Abstract, Medline) were searched using a combination of keywords. We included articles if they were primary studies published in the English language between 2007 and 2018, explored the issue of IPV perpetrated by male partners against their female partners, and discussed the issue of silencing. We excluded articles that focused on the elderly, adolescent, LGBTQ, or indigenous populations or if they focused on forced marriage, honor killing, or war violence. Quality assessment was done using Joanna-Briggs Institute critical appraisal tools.

Results

From 8264 non-duplicate citations, we included 21 articles for analysis following article screening by two reviewers. We categorized the factors influencing silencing into micro-,meso-, exo-, and macrosystem. Microsystem factors (such as but not limited to self-reliance, concern for family, and love for the perpetrator) was the most common influencer in reinforcing the silencing of affected women. Macrosystem (societal expectations, normalization of violence, gender norms, immigrations issues, religious values, and notion of an ideal family) played an integral role in shaping the factors in other subsystems. Women had to overcome significant microsystem and macrosystem barriers to contact the exosystem (healthcare providers, domestic violence agencies, and legal system) to share their problems.

Conclusion

Healthcare providers should recognize the courage summoned by affected women to overcome subsystem barriers before being able to contact them, as well as the ambivalence that is inherent in decisions with regards to IPV. Healthcare providers should develop insight into one's position in the ecological model and its effect on their interaction with affected women.

Abstract #: 10
Presenter: Ashley McCurdy
Supervisor: Margie Davenport
Title: Impact of prenatal exercise on both prenatal and postnatal anxiety and depressive symptoms: a systematic review and meta-analysis
Authors: Ashley McCurdy, Michelle Mottola, Rachel Skow, Victoria Meah, Veronica Poitras, Alejandra Jaramillo Garcia, Casey Gray, Nick Barrowman, Laurel Riske, Frances Sobierajski, Marina James, Taniya Nagpal, Andree-Anne Marchand, Megan Nuspl, Linda G Slater, Ruben Barakat, Kristi Adamo, Gregory Davies, Stephanie-May Ruchat, Margie Davenport
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Objective: Perinatal depression and anxiety are associated with adverse outcomes for mother and child. Standard treatment includes medication and psychotherapy; however, many women are reluctant to take medication during pregnancy and psychotherapy can be costly and difficult to access. Recent reviews have suggested that exercise is effective in treating mild to moderate depression and may be beneficial in reducing symptoms of anxiety, however, these effects have not been well studied in perinatal women. A recent systematic review and meta-analysis found that postnatal exercise improved mild to moderate depressive symptoms and reduced the odds of depression in the postnatal period. The current review aims to examine the influence of prenatal exercise on depression and anxiety during pregnancy and the postpartum period.

Methods: Online databases were searched up until January 6, 2017. Studies of all designs were included (except case studies) if they were published in English, Spanish or French and contained information on the Population (pregnant women without contraindication to exercise), Intervention (subjective or objective measures of frequency, intensity, duration, volume or type of exercise), Comparator (no exercise or different frequency, intensity, duration, volume and type of exercise) and Outcome (prenatal or postnatal depression or anxiety). Meta-analyses were performed separately by study design. Standardized mean differences (SMD) in post-intervention anxiety and depression scores were pooled using a random effects model. For dichotomous outcomes, inverse-variance weighting was used to obtain odds ratios (OR) using a random effects model.

Results: A total of 52 studies (n=131 406) were included. 'Moderate' quality evidence from randomized controlled trials (RCTs) revealed that exercise-only interventions, but not exercise + cointerventions, reduced the severity of prenatal depressive symptoms (13 RCTs, n=1175; standardized mean difference: −0.39, 95%CI −0.51 to −0.26, I^2 =11%) and the odds of prenatal depression by 67% (5 RCTs, n=563; OR: 0.33, 95%CI 0.21 to 0.53, I^2 =0%) compared with no exercise. Prenatal exercise did not alter the odds of postpartum depression or the severity of depressive symptoms in the postpartum period, nor anxiety or anxiety symptoms during or following pregnancy.

Summary/Conclusions: Prenatal exercise reduced the odds and severity of prenatal depression.

Funded By: CIHR

Abstract #: 11
Presenter: Maryam Kebbe
Supervisor: Geoff Ball
Title: Helping adolescents with obesity with lifestyle behavior change: Conversation cards for adolescents
Authors: Maryam Kebbe, Arnaldo Perez, Annick Buchholz, Tara-Leigh McHugh, Shannon Scott, Caroline Richard, Michele Dyson, Geoff Ball
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction. Health care providers (HCPs) report barriers to communicate with and support adolescents in weight management and may benefit from appropriate tools to complement their consultations. Since most adolescents with obesity do not meet minimum lifestyle recommendations, our team developed Conversation Cards for Adolescents, a clinical, bilingual tool to facilitate adolescent-HCP communication and help adolescents with lifestyle behaviour change.

Methods. Our research was completed between May 2016 and August 2018. It included three interrelated phases: (i) Conceptualization, (ii) Development, and (iii) Production and Knowledge Translation. Phase I included framing our research as cross-language (English and French) and patient-oriented studies. Phase II included a scoping review, an in-person patient engagement panel, 1-on-1 interviews, focus groups, an online prioritization activity, and a telephone data validation consultation with adolescents with obesity and/or HCPs from two weight management clinics in Edmonton and Ottawa. Steps in this phase were informed sequentially. Phase III included designing and refining our tool in collaboration with Obesity Canada.

Results. We identified 153 factors that help, may help, or deter adolescents with obesity from adopting healthy lifestyle behaviours. The top 15 priorities in each of these three categories were included in our tool (a hard-copy deck of cards) and were organized into the following suits: nutrition, physical activity, sedentariness, sleep, mental well-being, relationships, and clinical factors. Each card contains an individual statement pertaining to a barrier or enabler that adolescents encounter in making and maintaining healthy lifestyle changes (e.g., I have a hard time falling asleep because of my anxiety or nonstop thinking).

Conclusions. Our research has a direct impact on what and how health services are offered to adolescents with obesity in Canada. HCPs may use our tool to assist with counseling and individualizing treatment plans for and with adolescents with obesity.

Funded By: WCHRI Graduate Studentship; CIHR, Alberta Innovates; Alberta Health Services

Abstract #: 12
Presenter: Alyson Campbell
Supervisor: Shannon D. Scott
Title: The development and usability evaluation of a whiteboard animation video for acute otitis media
Authors: Alyson Campbell, Anne Le, Salima Meherali, Eleanor Fitzpatrick, Lisa Hartling, Shannon D. Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Acute otitis media (AOM) is the most common bacterial ear infection affecting up to 80% of children before the age of three. Despite the common occurrence of the illness and the wide range of material available at clinics and online, parents are not always aware of these resources. Furthermore, these resources do not appear to have any impact on service use when children are acutely sick, suggesting that more effective information sources are required. The purpose of this study is to work with parents to develop and assess the usability of a whiteboard animation video for AOM in children.

Methods: Semi-structured interviews were conducted with parents of children seeking care in an ED for AOM. These interviews informed the development of a whiteboard animation tool. Health care professionals and a Parent Advisory Group were consulted on the prototype and feedback was incorporated. A 3-minute video was developed that told the story of a young child afflicted by AOM and provided information on treatment and management strategies. The tool was evaluated by parents recruited from three rural ED waiting rooms in Nova Scotia, Canada. The usability survey contained 9, 5-point Likert scale questions assessing the user experience of the tool. Each answer was given a corresponding numerical score, with 5 being *strongly agree* and 1 being *strongly disagree*. Descriptive statistics and measures of central tendency were completed.

Results: 28 parents participated in usability evaluation of the whiteboard animation video. In general, parents' responses to the tool were positive (mean scores ranged from 4.1-4.59). All parents 'strongly agreed' or 'agreed' that the tool was simple to use, whether the tool could be used without written instructions or help, if the length was appropriate, and if the tool was aesthetically pleasing (mean scores were 4.53, 4.59, 4.43, and 4.50, respectively). Parents gave high scores when asked if they found the tool useful (mean = 4.39) and if the tool was relevant to them as parents (mean = 4.41). When asked about potential future usage of the tool, scores were 4.14 for both "I would use it in the future" and "it will help me make decisions about my child's health". Finally, when asked if parents would recommend the tool to a friend, parents gave a score of 4.25.

Conclusion: Parents were receptive to the whiteboard animation tool developed for AOM in children, indicating that is it highly usable.

Funded By: WCHRI Innovation Grant; Graduate Studentship; PaCET Award; CIHR

Abstract #: 13
Presenter: Yuliya Fakhr
Supervisor: Denise G Hemmings
Title: Lipid receptors as a novel pharmaceutical target for improving placental health in preeclampsia
Authors: Yuliya Fakhr, Jiabo Guo, Martina Mackova, Kristin Huntley, Denise Hemmings
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Background: Pro-inflammatory cytokines increase in preeclampsia (PE), a hypertensive pregnancy disorder. Factors released into maternal circulation from a poorly developed placenta play a critical role in PE development. Low fusion rates and increased cell death of placental trophoblasts by tumor necrosis factor-α (TNF-α), an inflammatory cytokine, lead to a poorly functioning maternal-fetal barrier that contributes to PE. Since blocking TNF-α to improve this barrier is not feasible due to its crucial role in fetal development, we investigate Sphingosine-1-Phosphate Receptor 2 (S1PR2), a receptor for the bioactive lipid sphingosine-1-phosphate (S1P), as a potential target. S1PR2 is overexpressed in the placentas of PE women. TNF-α signals through S1PR2 to induce cell death in endothelial cells; however, these effects in trophoblasts are unknown. We hypothesize that TNF-α will decrease trophoblast fusion and increase apoptosis in primary term trophoblasts. Blocking S1PR2 will reverse these TNF-α-mediated effects.

Methods: Cultured isolated trophoblasts were exposed to 0-20ng/mL of TNF-α for 24 hrs. Beta-human chorionic gonadotropin (β-hCG), a marker of trophoblast fusion, and lactate dehydrogenase (LDH) release, a marker of cell death, were measured with ELISA and LDH assay respectively. S1PR2 signaling was blocked using JTE-013 with and without 20ng/mL of TNF-α for 72 hrs. Exclusive S1PR2 signaling was achieved using VPC23019 to block S1PR1,3. β-hCG and LDH release were measured.

Results: TNF-α decreased β-hCG secretion 10–fold at 1-20 ng/mL after 24 hrs, and maintained this decrease till 72 hrs. TNF-α decreased LDH release to 60+/-5.8% at 1 ng/mL and increased release by 50+/-7.4 % at 20ng/mL at 24 hrs. In the presence of TNF-α, blocking S1PR2 did not increase β-hCG secretion to control levels (without TNF-α), blocking S1PR1,3 blocked β-hCG release, and blocking S1PR1-3 restored secretion to 50% of the control. No significant differences were observed between the inhibitor groups with or without TNF-α at 72 hrs, except for blocking S1PR2 in TNF-α presence where LDH release increased 3.5-fold of the control.

Conclusions: Exposure of primary trophoblasts to TNF-α increases cell death in a dose-dependent manner and blocks β-hCG release. Inhibiting S1PR2 signaling in the presence of TNF-α does not restore barrier formation to control levels, thus TNF-α does not operate through S1PR2 in this process; however, S1PR2 is necessary to maintain cell viability. Blocking S1PR1,3 in the absence of TNF-α blocks β-hCG secretion. This suggests that endogenous S1P binding to these receptors is a requirement for these cells to differentiate.

Funded By: CIHR; MatCH program funded by the Provost at the University of Alberta

Abstract #: 14
Presenter: Chenxi Cai
Supervisor: Margie Davenport
Title: Iron transport in human lactating epithelial cell
Authors: Chenxi Cai, Peter Eck, James Friel
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction/Objectives : Iron deficiency anemia in infants and toddlers is associated with lifelong attenuated cognitive and behavioral functioning. The capacity of milk to provide an adequate supply of iron is critical to breastfed infants as human milk is often the sole source of iron during early infancy. However, as the iron concentration of human milk is low, as many as 15% of all breast-fed infants developing anemia by 8 months of age. Mechanisms regulating iron transfer from the maternal circulation into human milk are not known.

Methods/Approach: In the present study, we collected human breast milk samples from nine lactating women (4 to 6 months postpartum) to study the gene expression profiles of iron transporters and iron binding proteins in the human lactating mammary gland.

Results/Findings: The mRNA extracted from human milk fat globule was confirmed mainly from epithelial cells by examining the expression of epithelial markers (Mucin 1). The expression of transferrin receptor 1(TFRC), divalent metal transporter 1 (DMT-1), transferrin (TF) and lactoferrin (LTF) were detected in lactating human epithelial cells.

A potential iron transport pathway in lactating human mammary epithelial cell was proposed based on the gene expression profiles: extracellular iron in serum is exclusively bound to TF; TF binds to TFRC in membranes and enters the endosome as a TF-TFRC complex; the iron is released from the complex by endocytosis, transported by DMT1, and incorporated into LTF via the ER-Golgi pathway; the iron-binding LFT is secreted into milk by secretory vesicles.

Conclusions: In conclusion, we present transcript-based evidence for the iron uptake and excretion pathways in the human mammary epithelial cell, suggesting known cellular uptake pathways, but a lack of capacity for transmembrane excretion. The only means of secretion into the breast milk might be via an iron-LTF complex. The data, however, do not rule out a complete lack of iron excretion capacity into human milk.

Funded By: CIHR

Abstract #: 15
Presenter: Afshin Namdar
Supervisor: Shokrollah Elahi
Title: Cord blood CD71+ erythroid cells promote HIV replication/infection and may impact mother to child transmission
Authors: Afshin Namdar, Petya Koleva, Michael Hawkes, Shokrollah Elahi
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction- Infectious diseases are the leading cause of death in the perinatal period. Susceptibility to infections during this period has been generally regarded as the immaturity of the immune system. However, we have challenged this notion by showing the presence of active immunosuppression in newborns. In line with this, we demonstrated the physiologically enriched $CD71^+$ erythroid cells (immature red blood cells) in the newborns and human cord blood with potent immunosuppressive properties. However, the potential effects of these cells in HIV infection in particular mother to child HIV transmission have not yet been determined. Herein, we sought to investigate whether human cord blood $CD71^+$ erythroid cells impacts HIV infection/replication in cord blood $CD4^+$ T cells.

Methods- The $CD71^+$ erythroid cells and $CD4^+$ T cells were isolated from healthy deliveries cord blood using magnetic cell sorting. Phytohemagglutinin and IL-2 activated purified $CD4^+$ T cells were infected with the CXCR4-utilizing isolate LAI strain of HIV virus using magnetofection and cocultured in the presence/absence of $CD71^+$ erythroid cells for 3 days. The cells were then stained with fluorescent-labeled antibodies and acquired with flow cytometry to evaluate the HIV infection in $CD4^+$ T cells. In some experiments, samples were collected for RNA sequencing and RT-PCR analysis.

Results- Our results for the very first time indicated that human cord blood $CD71^+$ erythroid cells exacerbates HIV infection in $CD4^+$ T cells through reactive oxygen species (ROS) production. These data coupled with RNA sequencing determined that ROS production negatively regulates the cell cycling machinery to facilitate the HIV replication. Moreover, we observed that cord blood $CD71^+$ erythroid cells expresses Duffy antigen receptor for chemokine (DARC) which acts as an HIV repository. Thus, DARC indirectly aggravates HIV infection and/or replication.

Conclusion- In conclusion, for the first time, we have shown that human cord blood $CD71^+$ erythroid cells play expand HIV infection and may impact HIV pathogenesis during the perinatal period. Our findings open a novel insight into the biology of these cells in HIV infection during pregnancy with possible impact on mother to child transmission of the virus.

Funded By: WCHRI Innovation Grant

Abstract #: 16
Presenter: Ashley Demsky
Supervisor: Helen Steed
Title: The Edmonton Obesity Staging System to predict mode of delivery in parturients, with overweight or obesity, who are undergoing an induction of labour
Authors: Ashley Demsky, Shawna Stafford, Daniel Birch, Arya Sharma, Jane Schulz, Helen Steed
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

There is a growing body of literature outlining the adverse consequences of excess body-weight in pregnancy. In particular, this has demonstrated an increased rate of cesarean delivery. The risks of cesarean delivery are further compounded should a woman require a cesarean delivery after a failed induction of labour. To date, there is no risk stratification tool to determine which women, with obesity and who are undergoing an induction of labour, are at the greatest risk of cesarean delivery. The Edmonton Obesity Staging System (EOSS) is an objective tool that uses weight and obesity-related co-morbidities to modify risk profiles. This study aims to validate the use of a modified EOSS to predict mode of delivery amongst nulliparous women, with overweight or obesity, who are undergoing an induction of labour at term. We hypothesize that there will be a higher likelihood of cesarean delivery in women assigned a higher EOSS stage.

Methods

A prospective-cohort study was performed from January to August 2018 at two high obstetrical volume centers in Edmonton, Alberta: The Lois Hole Hospital for Women and the Grey Nuns Hospital. A total of 345 women, undergoing an induction of labour at term, were recruited into the study. Women participating in the study provided a self-reported health survey and allowed for review of their medical records. The sample population included women with a BMI of ≥25.0 at first antenatal visit. Two independent evaluators assigned an EOSS stage and delivery records were reviewed postpartum. The primary outcome for this study is the rate of cesarean delivery.

Results

Overall, 345 women were recruited into this study with a participation rate of 93.7%. This included a sample group of 276 women, with overweight or obesity, and a control group of 69 normal-weight women. Data is currently undergoing statistical analysis.

Conclusion

A modified version of the EOSS may help stratify the risk of cesarean delivery in nulliparous women, with overweight or obesity, who are undergoing an induction of labour. In particular, the risk of cesarean delivery may increase in women assigned a higher EOSS stage.

Funded By: WCHRI Support services

Abstract #: 17
Presenter: Shruti Shah
Supervisor: Sandra Davidge
Title: Effects of placenta-specific nanoparticle encapsulated antioxidant delivery on placental oxidative stress in a rat model of fetal hypoxia
Authors: Shruti Shah, Esha Ganguly, Anita Quon, Jude Morton, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Pregnancy complications leading to fetal hypoxia are linked to the development of adult cardiovascular disease in offspring. We have shown that a prenatal hypoxic insult induces placental hypoxia and increases oxidative stress in the placenta, associated with fetal growth restriction. Oxidative stress arises when there is excess production of reactive oxygen species and a decrease in endogenous antioxidant defenses such as superoxide dismutase (SOD). MitoQ is an antioxidant which, when encapsulated in nanoparticles (nMitoQ), can be used to treat placental oxidative stress without crossing the placental barrier (thus preventing off-target treatment effects on the fetus). We hypothesized that maternal treatment of nMitoQ will prevent hypoxia-induced oxidative stress and increase endogenous antioxidant protection in the placenta; ultimately preventing the development of adult cardiovascular disease in the offspring.

Methods

Pregnant rats were exposed to either hypoxia (11% O_2) or normoxia (21% O_2) from gestational day (GD) 15-21 (term=22 days). On GD15, rats were intravenously injected with saline or nMitoQ. On GD21, placental tissue was collected from male and female pups. Cytosolic and mitochondrial superoxide (O_2^-) production was measured as an index for oxidative stress using DHE and MitoSOX staining respectively. Placental SOD (SOD1 and SOD2) expression was assessed by Western blotting. Statistical analysis was performed using a two way ANOVA.

Results

Prenatal hypoxia increased cytosolic O_2^- in male (normoxia: 0.021±0.001a.u. vs. hypoxia: 0.03±0.002a.u.; $p<0.05$) and female (normoxia: 0.021±0.001a.u. vs. hypoxia: 0.026±0.001a.u.; $p<0.05$) offspring placentas. nMitoQ treatment reduced cytosolic O_2^- in both male and female offspring. Prenatal hypoxia increased mitochondrial O_2^- in placentae of male offspring only (normoxia: 0.021±0.001a.u. vs. hypoxia: 0.025±0.001a.u.; $p<0.05$). nMitoQ reduced mitochondrial O_2^- in prenatally hypoxic placentae of female offspring only. Placental SOD1 expression was reduced by hypoxia in only male (normoxia: 1.407±0.345a.u. vs. hypoxia: 0.853±0.037a.u.; $p<0.05$) offspring and tended ($p<0.06$) to be reduced by nMitoQ in normoxic male offspring. SOD2 expression was not different between the groups.

Conclusion

nMitoQ treatment reduced mitochondrial O_2^- in hypoxic-exposed placentas from only female offspring suggesting a sexually dimorphic effect of nMitoQ, although cytosolic O_2^- was decreased in both sexes with nMitoQ treatment. Interestingly, prenatal hypoxia resulted in reduced endogenous cytosolic (SOD1) antioxidant expression in only male offspring, however nMitoQ did not alter this effect. The possible reduction of SOD1 in normoxic male placenta warrants further investigation. Our study highlights the importance of understanding sex differences in placentas from male and female offspring in developing treatment strategies for improving pregnancy outcomes.

Funded By: WCHRI Summer Studentship; Motyl Endowment Cardiac Sciences Summer Studentship Award

Abstract #: 18
Presenter: Danae Keddie
Supervisor: Stephane Bourque
Title: Perinatal iron deficiency combined with a high salt diet causes sex-dependent alterations in blood pressure and kidney morphology.
Authors: Danae Keddie, Andrew Woodman, Richard Mah, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Perinatal iron-deficiency (ID) is known to impact fetal and neonatal growth trajectories, which alters organ development and function. Adult offspring of ID mothers develop hypertension and salt-sensitivity, indicating a reduced capacity to handle excess sodium and fluid filtration. Here, we sought to assess the effects of perinatal ID on kidney morphology in the adult offspring, and whether any programming effects by ID are exacerbated by high salt intake.

Hypothesis: We hypothesize that perinatal ID causes long-term changes in renal morphology, characterized by glomerular basement membrane thickening and collagen deposition. We further hypothesize that these morphological features will be more pronounced in adult perinatal ID offspring fed a high salt diet.

Methods: Pregnant Sprague-Dawley rats were fed an iron-restricted diet to induce a state of iron deficiency during gestation, alongside control rats fed iron-replete diets. At postnatal day 138, offspring were fed either a high-salt diet (HS) or normal-salt (NS) diet for 6 weeks. On postnatal day 180, tissues were collected *postmortem*, and frozen kidneys were cryo-sectioned for morphological assessments. Masson's Trichrome stain was used to stain for collagen deposition, glomerular size and density. Jone's Methenamine Silver stain was used to assess basement membrane thickness.

Results: ID resulted in 34% and 52% decreases in maternal and offspring hemoglobin levels versus controls at birth. Blood pressure was significantly increased by both ID and HS in male six-month-old offspring ($P < 0.05$), but not in females. Adult male ID offspring were smaller than their control counterparts ($P<0.01$), albeit kidney size (normalized to body weight) was not affected by either ID or HS in either sex. Glomerular size was significantly increased in the male ID+HS group ($P<0.05$), with no changes in glomerular density due to either ID or HS. Interestingly, in female offspring, HS treatment was associated with an increase in glomerular density ($P<0.01$), with no significant changes in glomerular size. Male offspring exhibited increased glomerular basement membrane thickness due to both ID and HS (both $P<0.05$), whereas no alterations were evident in female offspring. Similarly, male offspring exhibited an increase in cortex collagen deposition due to both ID and HS ($P<0.05$) as well as increased medullary collagen deposition in the HS groups ($P<0.05$), while there were no significant changes in female offspring.

Conclusions: These findings indicate that perinatal ID combined with a HS diet alters blood pressure and renal morphology in the offspring, and this occurs in a sex-dependent manner.

Funded By: WCHRI Innovation Grant; CIHR; Alberta Innovates; Canadian Foundation for Innovation and Advanced Education

Abstract #: 19
Presenter: Kassi Boyd
Supervisor: Shanon Phelan
Title: A family's experiences of (in)dignity in leisure settings: implications for understanding disability, inclusion and child-driven culture
Authors: Kassi Boyd, Donna Goodwin, Shanon Phelan
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Dignity encompasses feelings of self-worth. These feelings can be shattered by the cruel acts of others, resulting in humiliation Children with autism experience increased rates of indignity over other children through physical, verbal, and relational bullying, often in public settings, including leisure contexts. Feelings of being 'lesser than' also extend to family members. The purpose of the study was to understand: *How is dignity experienced by a family with a child with autism as they engage in community-based family leisure?*

Approach

An interpretative phenomenological analysis case study was completed. The experiences of four family members across three generations were captured: Mom, Dad, Grandma, and Great-Grandma. Data were collected through two semi-structured interviews, conversational interviews, and researcher field notes. Interviews were transcribed verbatim and all data were subjected to thematic analysis. The conceptual framework of Relational Ethics facilitated the interpretation of the findings.

Results

The family experienced different types, levels, and violations of dignity during family leisure. Dignity was cyclically maintained, lost, and regained. Thematic analysis revealed four themes (a) living under a microscope - the family's early experiences were fraught with feelings of being singled out, (b) screw your microscope: we're going anyway - over time, the family chose to reject stranger imposed indignities and maintained participation in family leisure, (c) stories of belonging - the family members experienced dignity through engaged interactions, and (d) feeling overlooked: lamenting the future- as their son aged, he and his family were once again ignored and dismissed by others in the community.

Conclusions

Dignity occurred along a shifting continuum from the dignified to the undignified self. To experience inclusive leisure the family members extended considerable emotional labor and effortful planning to ensure successful outings. Their stories may provide leisure practitioners, researchers, families, and the general public with insights into the creation of dignified experiences of family leisure.Future research directions should focus on the perspectives of children experiencing autism. Specifically, it is important to understand experiences of inclusion in child-driven culture, from the perspectives of children. My proposed doctoral work will take a deeper look at the experiences of inclusion in (and exclusion from) child-driven culture for children living with autism. The research will be framed by one exploratory question: *How is inclusion/exclusion experienced by children with autism as they (dis)engage with child-driven culture?*

Funded By: WCHRI Graduate Studentship; Various Graduate Scholarships (will be recognized verbally and with logos where applicable)

Abstract #: 20
Presenter: Osnat Wine
Supervisor: Alvaro Osornio Vargas
Title: What are the essential components and mechanisms for interdisciplinary and collaborative research? Findings from the DoMiNO project
Authors: Osnat Wine, Jude Spiers, Katharina Kovacs Burns, Michael van Manen, Alvaro Osornio Vargas
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction:

Interdisciplinary and collaborative research approaches can address complex environmental health questions. However not much is known about what can optimize these approaches. It was this interest which was explored as part of the interdisciplinary Data Mining & Neonatal Outcomes (DoMiNO) project (2013-2018). The project examined relationships between mixtures of industrial pollutants and adverse birth outcomes, while applying integrated knowledge translation, through the participation, expertise, and perspectives of researchers, clinicians, and knowledge-users.

Methods:

To better understand collaborative, interdisciplinary research, we used qualitative case study methods to identify essential components that supported the interdisciplinary environmental research team. We used the DoMiNO project as an exemplar case study of collaborative research. Throughout the 5-year case study, multiple strategies were used to generate data including interviews, focus group, surveys, project documents, and observation. The partial findings presented here refer to a focus group that was held at the end of the project with ten members of the DoMiNO team. The discussion focused on the team's learnings from their own collaborative experience with the DoMiNO project. The discussion was recorded and transcribed verbatim. Thematic analysis procedures were applied including triangulation, comparison and verification with other data sources.

Findings:

We identified that developing the team and individuals' capacity is enabled through the evolution of building trust, commitment, and ownership. These were enabled by different mechanisms which were acknowledged by the team and include: keeping open channels for feedback and ongoing rapport; providing different opportunities for engagement, participation and learning; ensuring repetition of backgrounds, methods and processes in an inclusive and supportive environment; leadership commitment to the collaborative process; motivators (e.g. roles, results, celebrating success) as well as the need to balance commitments and perspectives, be flexible, patient and open minded. These mechanisms built relationships, enabled learning, and created bridges between team members and disciplines towards co-production and KT.

Conclusions:

It is important to acknowledge team processes, which can enable and improve team performance and research outcomes. Interdisciplinary and collaborative research is a long and complex journey and is vulnerable to challenge by its nature and context. The components and mechanisms described support the collaborative research process, and in our case resulted in a worthwhile experience which provided exciting results including knowledge translation and exchange activities with researchers and knowledge users.

Funded By: WCHRI Graduate Studentship; PaCET; Trainee Travel Grant; CIHR; NSERC, TD Bank Financial Group Grant for Health Sciences Interdisciplinary Research Fund Studentship

Abstract #: 21
Presenter: Charlene Nielsen
Supervisor: Alvaro Osornio Vargas
Title: Associations of critically ill small newborns and industrial air pollutants in space and time
Authors: Charlene Nielsen, Carl Amrhein, Prakesh Shah, Dave Stieb, Alvaro Osornio Vargas
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Critically ill small for gestational age (ciSGA) newborns are those who are admitted to neonatal intensive care units (NICU) and have a birthweight below the 10th percentile for gestational age and sex according to Canadian normative data. These are life-threatening and costly events requiring further understanding of risk factors. We assessed spatiotemporal hot spots of ciSGA and industrial air emissions, an infrequently studied source of shared exposures.

Methods: Using neonatal admission data from participating NICUs in the Canadian Neonatal Network (CNN) between 2006 and 2010, we aggregated the mother's residential postal codes for nineteen census metropolitan areas (CMA) into space-time cubes and applied emerging hot spot analyses. Using National Pollutant Release Inventory (NPRI) data and Environment Canada weather station data, we estimated monthly dispersion of air emissions in these areas. We compared the resulting patterns using logistic regression, with covariates for low socioeconomic status, traffic pollution, and the total number of infants during the study period.

Results: The larger CMAs had more and larger hot spots of ciSGA in space and time. Seventy eight industrial chemical hot spots were associated with ciSGA hot spots. The greatest number of positive associations were observed for 28 different pollutants, mostly in Edmonton, Halifax, Montréal, Toronto, Vancouver, and Winnipeg. Twenty one of those chemicals were known or suspected developmental toxicants, such as particulate matter, carbon monoxide, heavy metals, and VOCs.

Conclusion: Hot spot patterns of ciSGA differed among CMAs. Associations with hot spots of industrial chemical emissions were geographically specific and may help explain the space-time trends of ciSGA.

Funded By: CIHR; NSERC

Abstract #: 22
Presenter: Vanessa Carias
Supervisor: Rachel Wevrick
Title: Clinical and genetic analysis of children with a dual diagnosis of Tourette syndrome and autism spectrum disorder
Authors: Vanessa Carias, Rachel Wevrick
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction Gilles de la Tourette Syndrome (TS) is a neurodevelopmental disorder that causes children to make repeated, brief involuntary movements or sounds. While there is a strong genetic contribution to TS, few susceptibility genes have been identified. Children with TS often have other psychiatric disorders, such as obsessive-compulsive disorder, attention deficit hyperactivity disorder, or autism spectrum disorder (ASD). Clusters of biologically related genes have been associated with neurodevelopmental disorders, suggesting shared pathologies. The purpose of this study was 1) to identify and clinically characterize probands in the Simons Simplex Collection with a dual diagnosis of TS and ASD (TS/ASD) compared to those with ASD but not TS, 2) to analyze *de novo* genetic variants in TS/ASD probands including copy number variants, likely gene disrupting mutations, and missense mutations, and 3) to detect enrichment for biological pathways that could contribute to the pathogenesis of TS.

Methods We compared clinical data from children in the Simons Simplex Collection who carry a dual diagnosis of TS and ASD to children who have ASD but not TS. We performed gene set enrichment analysis on *de novo* genetic events in children with both TS and ASD to identify candidate genes and pathways, and compared these genes and pathways with those previously identified in TS using the Cytoscape pathway analysis tool.

Results Children with TS and ASD were diagnosed at an older age, had higher IQ scores, and had more restricted and repetitive behavior than children with ASD but not TS. Gene Ontology analysis revealed that proteins important for specific biological pathways, including regulation of calcium ion-dependent exocytosis, basement membrane organization, and visual behavior and learning, and specific cellular pathways, including basal lamina and ciliary transition zone, are enriched among genes with *de novo* mutations in children with TS and ASD.

Conclusions Clinical and genetic analysis of cohorts of affected children can help to determine the underlying pathophysiology of TS and other neurodevelopmental disorders. Expanding the number of dual diagnosis children with ASD and other medical findings from whom clinical and genetic data have been collected will be key to understanding how genes control intersecting developmental biological pathways, in turn leading to better therapeutics for these conditions.

Funded By: WCHRI Innovation Grant

Abstract #: 23
Presenter: Alison Thompson
Supervisor: Shannon D. Scott
Title: Understanding parents' experiences with childhood fever: A qualitative descriptive study
Authors: Alison Thompson, Anne Le, Hannah Brooks, Shannon D. Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Episodes of fever are an expected occurrence during childhood and although most cases can be managed at home, fever is among the most common reasons for parents to seek urgent care for a child. Ensuring parents have the knowledge, support, and resources to care for a feverish child at home has the potential to improve outcomes for families and promote appropriate health service use. There is a longstanding body of evidence focused on quantifying parents' knowledge and skills; however, more comprehensive explorations of parents' experiences managing a child with fever are required. The purpose of this study was to investigate parents' experiences with childhood fever.

Methods: We employed qualitative descriptive approaches in this study. 13 parents from the Emergency Department (ED) of the Stollery Children's Hospital participated in semi-structured interviews. Interviews were recorded and transcribed verbatim. We followed thematic analysis methods to analyze the data.

Results: Preliminary analysis of the data resulted in 2 themes central to parent experience: 1) *Parents fear the unknown:* In general, parents described feeling comfortable managing their child's fever at home. However, if the fever was prolonged or occurred alongside other symptoms, parents described feeling "panic" and increased anxiety. Parents worried when previously successful techniques for managing fever, such as administering Tylenol or Advil and cool baths or compresses, were ineffective. Parents attributed the struggle to manage their child's fever and the "out of the ordinary" symptoms as the main reasons for seeking emergency care. 2) *Parents want more information*: Parents expressed a desire for more information regarding their child's condition, particularly at discharge from emergency care. Despite generally positive experiences in the ED, parents had many questions regarding the cause of their child's fever, how they could make their child comfortable at home, and what actions to take should their child's condition become worse. Additionally, parents wanted more information on how to assess their child's condition, temperature guidelines for different age groups, and explanations on the tests and procedures performed during their child's hospital stay.

Conclusion: Although fever is an expected occurrence during childhood, parent experiences managing fever and associated symptoms can lead to feelings of fear and confusion. Providing parents with support and education on how to assess and manage a child's condition at home and when to seek emergency care are needed.

Funded By: WCHRI Graduate Studentship

Abstract #: 24
Presenter: Alexis Fong-Leboeuf
Supervisor: Dr. Debra Andrews
Title: Developing skills for developmental disabilities: Clinical experience as an adjunct to current preclinical curriculum improves student confidence
Authors: Alexis Fong-Leboeuf, Andy Le, Irina Simin, Debra Andrews
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction:

Medical students feel they have inadequate training in caring for patients with developmental disabilities (PWDD) and behavioural co-morbidities (Troller et al. 2016; Salvador-Carulla et al., 2015). Inadequate education regarding care of PWDD can lead to frustration and negative attitudes toward this complex patient population. Consequently, PWDD may not receive timely and empathetic care (Sahin & Akyol, 2010). Our preclinical 12-hour elective, "Developing Skills with Developmental Disabilities" (DSDD), has a primary learning objective of improving students' knowledge of and attitudes toward PWDD. The current study's objective was to compare confidence outcomes of DSDD students to those exposed only to the standard Neurosciences curriculum.

Methods:

The Developmental week in the mandatory pre-clinical Neurosciences block is comprised of didactic lectures on developmental disabilities, a problem-based learning case on developmental delay, and small-group clinical skills sessions with typically developing children and their parents.

DSDD elective students also received 6 hours of didactic teachings from developmental pediatricians and physiatrists on normal/abnormal child development, estimating developmental age, assistive technologies, and breaking bad news. Students spent 6 additional clinical hours at a rehabilitation hospital, where they attended a medical intake session, conducted a brief interview with the child's family, observed school-aged PWDD in a modified classroom, and interacted with the interdisciplinary team.

Participating DSDD students were given pre- and post-elective self-assessment surveys administered on a 5-point Likert scale. Questions pertained to students' self-perceived comfort and knowledge regarding PWDD. Control students received the same surveys at the beginning and end of the Neurosciences block. Scores pre- and post-elective were used to calculate relative improvement of controls and elective participants. T-tests were then used to compare these cohorts.

Results:

Data was collected from 2 consecutive years, including 35 students who completed DSDD and 18 control students from the same academic classes. Statistically significant ($p<0.05$) relative improvements were present in 4 of 10 self-reported scores, with the statistically significant scores pertaining to confidence interacting with PWDD, taking histories, recommending appropriate resources to families, and estimating developmental age.

Conclusions:

DSDD appears to teach skills that may not be learned from the standard Neurosciences curriculum. Improvement in confidence is a first step in implementing a new skill or changing a behaviour. Skills reported as improved included interacting with PWWD, approach to histories, recommending resources, and estimating developmental age. Next steps would be to see if these changes translate into improved clinical skills in practice and ultimately better care for this population.

Funded By: Medical Students' Association (MSA)

Abstract #: 25
Presenter: Jayani Abeysekera
Supervisor: Lisa Hornberger
Title: Accuracy of fetal echocardiography in the current era
Authors: Kim Haberer, Angela McBrien, Aisling Young, Jayani Abeysekera, Gayathri Wewala, Winnie Savard, Luke Eckersley, Timothy Colen, Lisa Hornberger
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Enhanced ultrasound technology and improvements in prenatal detection have facilitated fine-tuning fetal cardiac diagnoses. We sought to determine the accuracy of fetal echocardiography in defining anatomical details of major structural fetal heart disease (FHD).

Methods: Fetal echo databases at the University of Alberta were reviewed to identify pregnancies with major FHD between 2007-2018. We excluded simple septal defects, minor valve abnormalities, and isolated coarctation. FHD was divided into 12 major categories to examine differences between subtypes. Fetal echocardiography reports were compared to post-natal echocardiography or autopsy, to assess segmental anatomy. Differences were described as follows: 1) No difference between fetal and postnatal findings, 2) Minor differences with no impact on outcome, 3) Minor differences that could make a minor difference to the delivery plan or surgery, 4) Major differences that could change the pregnancy course, delivery or surgical planning, 5) Errors of categorization that would not alter surgery but could change counselling.

Results: 744 pregnancies with major FHD were identified: 524 (71%) live born, 151 (20.3%) underwent pregnancy termination, 43 (6%) had intrauterine demise, and 6 (1%) were lost to follow-up. Of the 744 pregnancies, 542 had confirmation of full cardiac anatomy (524 via echocardiogram and 18 autopsies). Table 1 details the number of cases where differences were demonstrated.

Conclusion: Fetal echocardiography in the current era is highly accurate with few serious errors. Delineating the anatomy of the outflow tracts in complex cardiac lesions remains a challenge.

Table 1. Number of Cases Per Lesion Subtype with Missed Pathology

Lesion Subtype	Confirmed/ Total	Category 1	Category 2	Category 3	Category 4	Category 5
HLHS/AS	91/132	81 (89%)	6 (7%)	0	2 (2%)	2 (2%)
TGA	62/63	58 (94%)	3 (5%)	0	1 (2%)	0
TOF/PA-VSD	100/142	73 (73%)	13 (18%)	10 (10%)	4 (4%)	0
Truncus Arteriosus	20/24	13 (65%)	1 (5%)	0	6 (30%)	0
PA/PS IVS	28/37	24 (86%)	1 (4%)	2 (8%)	0	1 (4%)
Ebstein/TVD	16/24	13 (81%)	0	2 (15%)	0	1 (7%)
AVSD	52/79	33 (64%)	13 (25%)	3 (6%)	3 (6%)	0
Tricuspid Atresia	19/23	14 (74%)	2 (11%)	2 (11%)	0	1 (5%)
Heterotaxy	46/69	29 (63%)	9 (20%)	4 (9%)	3 (6%)	1 (2%)
DORV	29/54	20 (69%)	3 (10%)	1 (3%)	4 (14%)	1 (3%)
Complex left heart lesions	58/71	38 (66%)	10 (17%)	8 (14%)	2 (3%)	0
Complex CHD/single ventricles	21/26	16 (76%)	2 (10%)	0	0	3 (14%)
TOTAL	542/744	412 (76%)	63 (12%)	34 (6%)	25 (5%)	10 (2%)

Funded By: Department of Pediatrics

Abstract #: 26
Presenter: Aisling Young
Supervisor: Angela McBrien
Title: Prenatal detection, comorbidities, and management of vascular rings: A 15-year regional study
Authors: Aisling Young, Lisa Hornberger, Kim Haberer, Deborah Fruitman, Lindsay Mills, Michelle Noga, Edythe Tham, Angela McBrien
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Vascular rings are caused by a variety of embryological abnormalities of the great arteries, which result in the trachea and esophagus being encircled by vascular structures. These historically present postnatally with respiratory or swallowing symptoms, making the need for surgery clear. The three vessel and trachea view evaluates arch sidedness and can be used to diagnose vascular rings prenatally. This view is now included in Canadian obstetrical screening guidelines. We hypothesized that the implementation of this view has increased prenatal diagnosis rates of vascular rings, resulting in an opportunity to better understand the natural history of this group of conditions.

Methods: We retrospectively reviewed trends in prenatal detection rates, precision of fetal echocardiography in diagnosing the anatomical sub-type, the frequency of associated anomalies (including genetic abnormalities), and clinical outcomes of patients with vascular rings diagnosed both prenatally and postnatally in the province of Alberta between 2002 and 2017.

Results: Of 106 patients with vascular rings, 28 (26%) had a prenatal diagnosis. Prenatal detection rates increased over time; 0/29 prior to 2009, 4/28 (14%) from 2009-2011, 7/23 (30%) from 2012-2014, and 17/26 (65%) from 2015-2017 ($p < 0.01$). The majority of cases had right aortic arch/aberrant left subclavian artery/left ductus arteriosus (77/106, 73%). Additional cardiac lesions were more common among prenatally detected cases (18/28, 64% vs 33/78, 42%; $p = 0.05$). The rate of genetic abnormalities was similar between groups and relatively high (11/28, 39% vs 25/78, 32%; $p=0.49$). Need for surgical repair was common and comparable between groups (23/28, 82% vs 66/78, 85%; $p = 0.76$). Those with prenatal diagnoses were less likely to require cross-sectional imaging (8/28, 29% vs 48/78, 62%; $p < 0.01$), which modified the vascular ring sub-type in only 2 patients.

Conclusions: This large cohort illustrates major improvement in prenatal detection of vascular rings over time. Surgery is required in the vast majority, irrespective of the timing of diagnosis. Children with a prenatal diagnosis have fewer non-diagnostic investigations. The diagnostic accuracy of echocardiography in both groups suggests additional imaging may not routinely be required. The relatively high rate of genetic abnormalities highlights the need for genetic counseling and screening at diagnosis.

Funded By: WCHRI Trainee Travel Grant

Abstract #: 27
Presenter: Kylie Bernstein
Supervisor: Sunita Vohra
Title: Massage therapy for pediatric procedural pain: a rapid review
Authors: Kylie Bernstein, Mohammad Karkhaneh, Liliane Zorzela, Hsing Jou, Sunita Vohra
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Pain management is a common pediatric problem. Children are frequently subjected to painful procedures, yet research has shown that procedural pain is sub optimally addressed, and among the most difficult type of pain to manage. Inadequately treated pain can have long term childhood consequences, including heightened pain sensitivity and negative effects on developmental outcomes. In an attempt to better manage procedural pain, complementary therapies are being sought as adjuncts to conventional pain management, including massage therapy. We assessed the evidence for use of massage therapy for acute procedural pain management in children.

Methods: We searched five main databases for (i) randomized controlled trials and controlled clinical trials, (ii) English language, (iii) children aged 0-18 years, (iv) massage as the intervention compared to standard care or placebo, and (vi) pain as a measurable outcome.

Results: Eleven pediatric trials of procedural pain in neonatal, burn and oncology populations were identified. Eight reported statistically significant reductions in pain after massage therapy compared to standard care alone. The studies were heterogeneous in population and techniques used. No adverse events associated with massage therapy were identified.

Conclusion: There is preliminary supportive evidence for massage therapy as an effective non-invasive adjunct for management of procedural pain in children. Further clinical trials within each sub-population with rigorous methodology would enhance the quality of evidence.

Abstract #: 28
Presenter: Lester Liao
Supervisor: Dawn Davies
Title: Palliative care in pluralistic societies: Digging deeper into a world of perspectives
Authors: Lester Liao, Keon Ma, Kiersten Schwann
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: As societies grow in diversity, medical practitioners are faced with the challenge of how to make decisions in a pluralistic environment. Disagreements between practitioners and patients can be pronounced in the end-of-life setting when various perspectives are involved in the decision-making process. In this context, many interventions are intended to practically increase cultural sensitivity. Nonetheless, to truly engage the increasing world of diversity and to have open discussion in an enduring manner, it is important to deeply examine the ideologies that are operative at a foundational level. In other words, what is at the heart of why we disagree and why do I hold the position that I hold? A favourable solution first requires an accurate diagnosis of the problem.

Methods: Understanding the development of perspectives that either physicians or patients have adopted requires a broadly, interdisciplinary approach that extends beyond the traditional scope of medicine. This presentation embraces insights from sociology, psychology, history, and philosophy, and translates them into an overview for practitioners to understand how the predominant bioethical frameworks applied at the end of life developed. These viewpoints are explored specifically through engaging the sociological theory of the secularization thesis, the psychology of moral foundations theory, the historical event of the Reformation, and the birth of philosophical existentialism.

Results: At its foundation, disagreements occur because of disparate worldviews. These are sets of beliefs that include answers to the questions of why we exist, where we come from, where we are going, and how we should live. In the North American context, many medical institutions adopt a secular, existential, and individualistic perspective on clinical medicine and ethics. This perspective has a particular philosophical heritage that undergirds it that is not universal. This contrasts with patients whose cultures differ from Western ideological trends, where notions of God and the sacred, duty, and community can shape ethics.

Conclusions: The predominant ethical frameworks employed by physicians in the West have a clear intellectual history and are not neutral. Recognizing personal biases and their etiology is an underexamined but crucial component and first step in clarifying discussions. Reviewing this material practically transforms the approach to end-of-life discussions, as it affords a level of humility through expanding ideological horizons and requires practitioners to be critical of their own assumptions. It also enables practitioners to engage issues at the core of disagreements and to seek solutions beyond superficial agreement or acrimonious endings.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant

Abstract #: 29
Presenter: Ratika Srivastava
Supervisor: Jerome Yager
Title: Patterns of injury in children with perinatal arterial ischemic stroke and infantile spasms
Authors: Ratika Srivastava, Oriana Shaw, Edward Armstrong, Francois-Dominique Morneau-Jacob, Jerome Y. Yager
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction:

Perinatal arterial ischemic stroke (AIS) is the most common stroke in children at an incidence of 1 in 4000 live births. Consequences include a spectrum of seizure disorders and cognitive and motor disability. Infantile spasms (IS) is an epileptic encephalopathy of infancy with an incidence of 2 per 10,000 live births. Approximately 5% of IS is caused by perinatal AIS. Patterns of ischemic injury that may predispose infants to IS and predict treatment response have not yet been identified.

Methods:

This retrospective case series of infants with AIS and IS provides detailed descriptions of ischemic distribution, seizure presentation, treatment and outcomes. Inclusion criteria were: term birth, ischemic stroke or encephalomalacia in an arterial distribution identified or presumed to have occurred in the perinatal period, and a clinical diagnosis of infantile spasms. Patients with a watershed pattern of injury were excluded. The modified pediatric ASPECTS was used as a measure of stroke severity to qualify and quantify stroke type and distribution. Areas of injury were identified on MRI and scored from T2/Flair or DWI sequences.

Results:

Eleven patients with AIS and IS were identified. Of nine who fit inclusion criteria, five had AIS diagnosed retrospectively after developing IS and four were diagnosed acutely in the neonatal period. All had MCA territory involvement with 67% having basal ganglia injury. Three presented with neonatal seizures and were the only three patients with complete right MCA infarcts including injury to the deep structures. Across all patients, the median ASPECTS was 11 (range 5-22). The highest ASPECTS (bilateral complete MCA) was associated with the worst outcome in motor function and epilepsy control. However, the second-highest ASPECTS (unilateral MCA, bilateral ACA) had mild motor deficits and no seizure recurrence after IS resolution. The three lowest ASPECTS (5,6,7) involved unilateral cortical MCA strokes sparing the deep structures. These patients also had the best motor outcome and seizure control.

Conclusions:

The co-occurrence of perinatal AIS and IS often results in significant neurologic disability. Although there was no defined pattern of regional homogeneity, there was a trend towards basal ganglia injury with progression of epilepsy after IS. This study highlights that size of ischemic injury may be less important than location as a predictor of motor outcome and seizure intractability. Future research will focus on identifying areas of injury that may confer increased risk of IS compared to stroke patients who remain seizure-free.

Abstract #: 30
Presenter: Bahareh Hamedi
Supervisor: Lynne-Marie Postovit
Title: Anti-cancer effects of n-3 long chain polyunsaturated fatty acids (LCPUFA) on ovarian cancer growth in vitro and in vivo.
Authors: Bahareh Hamedi, Olena Bilyk, Marnie Newell, Susan Goruk, Catherine Field
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

There is a strong rationale for studying nutritional interventions in cancer prevention and therapy. In this study, we evaluated the effect of n-3 LCPUFA on OC cell growth and sensitivity to carboplatin both *in vitro* and *in vivo*.

Methods and Results: *In vitro* assays were designed to assess cell growth, viability, fatty acid composition in lipid rafts and apoptotic-related protein expression (by metabolic MTT assay, gas chromatography, flow cytometry and western blotting, respectively) in 6 OC cell lines and normal ovarian and fallopian tube cells. Cells were treated with different concentrations of DHA (Docosahexaenoic acid) and OA (Oleic acid, used as a control) that would be achievable in blood serum by dietary intervention (10-320 uM). The effect of DHA seemed to be specific only to malignant ovarian cells. The inhibitory effect of DHA on the growth and viability was demonstrated in clear-cell carcinoma cell line ES2 while OC cells of other histological types were not sensitive to DHA. Pre-treatment with DHA increased the sensitivity of resistant OC cell lines A2780cp, ES2 and SKOV3 to carboplatin. We showed that DHA induced both early and late apoptosis in the DHA sensitive cell lines. Evaluation of different apoptotic pathway proteins and dead receptor CD95 expression is in progress.

For *in vivo* part of the study, we used patient-derived xenografts models (PDX) developed by transplanting human high-grade OC tissues into immune-compromised mice. After transplanted tumors reached 2-3mm^2, mice were randomly assigned into four groups: basal diet, basal diet plus carboplatin treatment, DHA diet and DHA diet plus carboplatin treatment. We determined that DHA enriched diet significantly reduced the tumor growth compared to control basic diet. Furthermore, DHA enriched diet significantly increased the sensitivity of PDX tumors to carboplatin treatment and reduced toxicity associated with chemotherapy. Histological evaluation showed that combination of DHA diet with carboplatin treatment increased the area of necrosis in tumors compared to control group. To evaluate the mechanism of DHA on PDX tumors, the expression of proliferation and dead receptor markers, as well as cellular DNA fragmentation will be assessed by IHC.

Conclusion. *In vitro* and *in vivo* evidence of DHA efficacy on OC cell growth was demonstrated. DHA might increase the sensitivity of OC cells to platinum-based chemotherapy. Further studies, as well as clinical trials are necessary to provide a strong rationale for a targeted n-3 PUFA intervention to be considered as an adjuvant to antineoplastic drug therapy of OC.

Funded By: Antoine Noujaim

Abstract #: 31
Presenter: Zelei Yang
Supervisor: David & Denise Brindley & Hemmings
Title: Cytomegalovirus infection enhances breast cancer metastasis in mice
Authors: Zelei Yang, Xiaoyun Tang, Matthew Benesch, Martina Mackova, Denise Hemmings, David Brindley
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Cytomegalovirus (CMV) infects 40-70% of women but has been reported in >90% of breast cancer patients. Breast tumors cause inflammation, which stimulates autotaxin (ATX) secretion from surrounding adipose tissue. ATX produces lysophosphatidate, which causes further inflammation in a feed forward cycle that promotes tumor growth and metastasis. Our preliminary results from treating human breast adipose tissues and breast cancer cells with human CMV in culture showed increased gene expressions of inflammatory stimuli like interleukin-6 and cyclooxygenase-2. We hypothesized that CMV infection would enhance the inflammatory cycle in the breast and promote tumor growth and metastasis.

Methods

A syngeneic mouse breast cancer model was established by injecting 4T1 breast cancer cells into the mammary fat pad of Balb/c mice. A transgenic MMTV-PyVT mouse model with spontaneous tumor growth was also used. Mice were either infected with mouse CMV (mCMV) or mock infected (virus removed by filter) 10 weeks prior to tumor inoculation or spontaneous tumor development to establish a presumed latent infection status. Tumor growth was monitored by caliper measurements at regular intervals. Tumor volume, mass and morphologies were determined at the endpoint. Lung metastasis was examined by counting the nodules on the lung surface or staining for micro-metastasis. Breast tumors and lung metastatic nodules were examined by immunohistochemistry for the proliferation marker, Ki67.

Results

mCMV infection had minimal effect on the volume and mass of the breast tumors developed in the mouse models, but it enhanced metastasis. In the Balb/c mice, mCMV infection led to a 3-fold increase in the number of surface lung nodules. mCMV-infected MMTV-PyVT mice had a 2-fold more nodules with a 6-fold greater area in the stained lung sections compared to uninfected controls. Ki-67 staining for proliferation in breast tumor sections from MMTV-PyVT mice was not significantly different between infected and uninfected mice. However, in the lung metastatic nodules, the percentage of Ki67-positive cells was increased by 2-fold in mCMV-infected mice. mCMV-infected MMTV-PyVT mice also developed tumors that had worse phenotypes than the uninfected mice, including more multiple-lobed tumors that contained more blood.

Conclusions

This work examines the effect of CMV infection on breast tumor growth and metastasis using mouse models that resemble the human physiological situation. My results illustrate that CMV infection had little effect on tumor growth, but it promoted breast cancer metastasis. This is crucial since it is not the primary tumor that kills breast cancer patients, but the metastasis.

Funded By: WCHRI Innovation Grant; Canadian Breast Cancer Foundation and Breast Cancer Society of Canada

Abstract #: 32
Presenter: Huachen Chen
Supervisor: Yangxin Fu
Title: Transcription factor ZIC2 promotes tumorigenic phenotypes in epithelial ovarian cancer
Authors: Huachen Chen, Krista Vincent, Zhihua Xu, Lynne-Marie Postovit, Yangxin Fu
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Objectives

Epithelial ovarian cancer (EOC) is the leading cause of gynecological cancer death in women. Current therapeutic regimens are ineffective against advanced EOC due to the recurrence of the disease and acquired chemoresistance driven by cancer stem cells (CSCs). A combined therapy that targets both bulk cells and CSCs would be a more effective therapeutic strategy to manage and/or prevent recurrent and resistant disease. Transcription factor ZIC2 has emerged as an oncogenic factor in various types of cancer. This project aims to investigate the pro-tumorigenic role of ZIC2 in EOC and the underlying mechanisms.

Methods

Association of ZIC2 expression with survival of EOC patients was determined by analyzing TCGA (The Cancer Genome Atlas) dataset. ZIC2 expression was examined in a panel of EOC cell lines of different histotypes at protein level. ZIC2 knockout via CRISPR or overexpression models were generated in EOC cell lines. The effect of ZIC2 knockout or overexpression on gene expression and the percentage of CSCs was determined by Western blotting and/or quantitative (q)RT-PCR analysis and ALDEFLUOR™ assay, respectively. The functional impact of ZIC2 knockout or overexpression was examined on growth (neutral red uptake assay), migration (scratch assay), anchorage-independent growth (soft agar assay), self-renewal (limiting dilution sphere formation assay) and tumor formation (subcutaneous xenograft model in the immunodeficient mouse) of EOC cells.

Results

The TCGA database analysis indicates that higher ZIC2 mRNA expression is associated with shorter survival of EOC patients. Knockout of ZIC2 in the ZIC2-positive EOC cell lines results in decreased growth (only after cells became confluent), cell mobility, anchorage-independent growth, sphere-forming ability and tumor formation in the mouse subcutaneous xenograft model. Mechanistically, ZIC2 knockout decreased the expression of CSC-associated genes, such as Oct4, NANOG, ALDH1A1at protein levels, which was restored by re-expression of ZIC2. In keep with ALDH1A1 expression, ZIC2 knockout dramatically decreased the $ALDH^{high}$ population (a known population enriched for CSCs in EOC), whereas ZIC2 overexpression increased the $ALDH^{high}$ population compared to their respective controls. Sphere formation assay confirmed that $ALDH^{high}$ cells isolated from ZIC2 knockout cells lost $ALDH^{high}$ population faster than those isolated from ZIC2 wild-type cells, indicating a role for ZIC2 in maintaining the CSCs in EOC.

Conclusions

Our *in vitro* and *in vivo* work indicates that ZIC2 promotes tumorigenic phenotypes through regulating the biology of the bulk cells and maintaining CSCs in EOC, suggesting that ZIC2 is a promising therapeutic target for EOC.

Funded By: WCHRI Innovation Grant

Abstract #: 33
Presenter: Olena Bilyk
Supervisor: Lynne Postovit
Title: Embryonic protein Nodal as a novel marker of progression and drug resistance of ovarian cancer
Authors: Olena Bilyk, Laura Lee, Linda Cook, Nhu D. Le, Martin Koebel, Lynne Postovit
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction. Cancer cells can exploit normally dormant embryonic stem cell pathways to promote cancer progression and metastasis. Studying embryonic signaling pathways in aggressive cancer has led to the discovery of the re-expression of the embryonic protein Nodal. Nodal, an embryonic morphogen belonging to the TGF-β superfamily of secreted signalling factors, maintains pluripotency and cell plasticity of human embryonic stem cells. In many cancers Nodal signalling promotes tumor growth and metastasis. *The objective of this study is to investigate the role of Nodal in ovarian cancer (OC) cell plasticity, progression and resistance to platinum/taxol chemotherapy*

Methods. We applied bioinformatics approach and RNA sequencing to explore the impact of Nodal on biological processes in OC cells and disease outcome. *In vitro* assays designed to assess growth, stem cell like phenotypes and chemoresistance in OC cell line A2780s wherein Nodal was added with Nodal expression construct, or knockout with CRISP/Cas9 genome editing were conducted. IHC staining to evaluate Nodal expression in high-grade serous OC (HGSOC) tissue microarrays was done.

Results. We discovered that Nodal induces transcriptional reprogramming in OC cells via altering immune response, metabolism and drug resistance gene expression. *In vitro*, we showed that OC cells overexpressing Nodal characterized by increased resistance to cytostatic drugs, tumorigenicity and cell plasticity (partial EMT and stem cell-like phenotype). The results of analysis of TCGA microarray data and IHC of microarrays of different histotypes of OC (OVAL BC cohort) showed the significant association of Nodal expression with HGSOC. Survival analysis determined that Nodal predicts poor overall and progression-free survival in HGSOC patients.

Conclusion. Nodal predicts poor survival in high-grade serous OC patients and likely drives tumorigenic potential and resistance to platinum in OC cells by promoting cancer stem cell plasticity and upregulating target genes involved in immune response, drug resistance and metabolism, and may hold promise as a therapeutic target to prevent OC recurrence.

Funded By: CIHR

Abstract #: 34
Presenter: Fahrin Rawji
Supervisor: Sue Ross
Title: Creating cost-conscious residents in Obstetrics and Gynecology: A randomised controlled trial
Authors: Fahrin Rawji, Allison Edwards, Maryna Yaskina, Sue Ross
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Residents have a professional obligation to the stewardship of healthcare resources yet there is a paucity of research on how to improve their cost-awareness. Rising health care expenditure has highlighted a critical need to improve education in this competency. This study aims to test if an educational module can teach residents to make cost-conscious management plans and reduce health care spending.

Methods: All Canadian Obstetrics and Gynecology residents in 2017 were eligible for this randomised controlled trial. The study was administered online via REDCap. Interested residents were enrolled, stratified by level of training and block randomised. Residents completed a survey to determine their management of four obstetrical scenarios. The intervention group reviewed an educational module on cost-effective ordering prior to completing the survey; the control group had the option to review it after. The primary outcome was mean total expenditure as calculated from the survey. Student's t-test was used to compare the mean total expenditure between the two groups.

Results: 85 residents were enrolled, 63 residents completed study requirements (30 intervention and 33 control). Mean total expenditure was $291.03 CAD (95% confidence interval [CI] 259.38-322.68) versus $192.98 CAD (95% CI 170.67-215.29) in the control and intervention groups respectively, corresponding to a 33.69% or $98.05 CAD ($p$=0.0001) reduction in total expenditure.

Conclusions: This educational module decreased expenditure by Canadian Obstetrics and Gynecology residents in the management of hypothetical obstetrical cases. This introduces a potential curriculum innovation to improve resident education in judicious use of healthcare resources.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant

Abstract #: 35
Presenter: Christa Aubrey
Supervisor: Sophia Pin
Title: Endometrial cancer and bariatric surgery: A scoping review
Authors: Christa Aubrey, Kristin Black, Sandy Campbell, Sophia Pin
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction/Objectives: Endometrial cancer is strongly associated with obesity, and weight reduction has been demonstrated to decrease risk and overall mortality. Our objective was to conduct a scoping review of the published literature of effects of bariatric surgery on endometrial cancer, as risk reudction and potential adjunct to treatment.

Methods/Approach: A comprehensive search of peer-reviewed literature was conducted by an expert searcher/librarian to retrieve relevant articles discussing aspects of endometrial cancer or endometiral hyperplasia and bariatric surgery

Results/Findings: After screening, 23 articles met inclusion for review, categorized into evidence for risk reduction of bariatric surgery on endometrial cancer, the impact of bariatric surgery on endometrial pathology, immunohistochemistry, and metabolic profiles, and bariatric surgery as a potential adjunct to treatment in endometrial cancer.

Conclusion: There is ample evidence demonstrating a risk reduction in women with obesity (BMI>30kg/m^2) undergoing bariatric surgery for subsequent development of endometrial cancer. However, there is a paucity of data investigating its role as an adjunct for therapy. There is sufficent evidence to argue for inclusion of endometrial hyperplasia and endometrial cancer as obesity-related conditions and the access to bariatric surgery should be broadened for affected individuals to reflect this.

Abstract #: 36
Presenter: Brittany Matenchuk
Supervisor: Anita Kozyrskyj
Title: Prenatal depression and birth mode sequentially mediate maternal education's influence on infant sleep duration
Authors: Aaron P. van der Leek, Sarah Bridgman, Catherine J Field, Anne Hicks, Yarden Yanishevsky, Meghan B. Azad, Allan B Becker, Piushkumar J Mandhane, Malcolm R Sears, Stuart E Turvey, Theo Moraes, Padmaja Subbarao, James A Scott and Anita L Kozyrskyj , CHILD Study Investigators
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Sleep duration is critical to growth, learning, and immune function development in infancy. Strategies to ensure that national recommendations for sleep duration in infants are met require knowledge of perinatal factors that affect infant sleep.

Objectives: To investigate the mechanistic pathways linking maternal education and infant sleep.

Methods: An observational study was conducted on 619 infants whose mothers were enrolled at the Edmonton site of the Canadian Healthy Infant Longitudinal Development (CHILD) study birth cohort. Infant sleep duration at 3 months was assessed using the Brief Infant Sleep Questionnaire. Maternal education was collected via maternal report. Prenatal and postnatal depression scores were obtained from the 20-item Center for Epidemiologic Studies Depression Scale (CES-D). Birth records and maternal report were the source of covariate measures. Mediation analysis (PROCESS v3.0) was used to examine the indirect effects of maternal education on infant sleep duration mediated through prenatal depression and birth mode.

Measurements and Main Results: At 3 months of age, infants slept on average 14.17 hours. Lower maternal education was associated with 25 minutes shorter infant sleep duration per 24-hour period (p=0.014). Prenatal depression was associated with 34.8 minutes shorter sleep per 24-hour period (p=0.011). Emergency cesarean section birth was associated with 1-hour shorter sleep duration at 3 months compared to vaginal birth [without intrapartum antibiotic prophylaxis] (p=0.001). Mediation analysis found that the direct effect of maternal education on infant sleep duration did not remain significant when the indirect effects of prenatal depression and birth mode were included (Total Direct Effect: -0.27; 95% CI: -0.63, 0.09; p=NS). Thirty percent of the effect of lower maternal education on infant total sleep duration (Total Effects: -0.38, 95% CI: -0.74, -0.03, p=0.04) was mediated sequentially through prenatal depression and birth mode (Total Indirect Effects: -0.12, 95%CI: -0.22, -0.03, $p<0.05$).

Conclusions: Prenatal depression and birth mode sequentially mediate the effect of maternal education on infant sleep duration.

Funded By: CIHR

Abstract #: 37
Presenter: Han Lee
Supervisor: David Olson
Title: Leukocyte invasion in an IL1β-induced mouse model of preterm labour
Authors: Han Lee, Meghan Onushko, Sheena Fang, David Olson
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction. Leukocyte invasion of the maternal uterus is a parturition phenomenon that precludes term and preterm labour (TL, PTL). In TL, leukocyte invasion is regulated by the secretion of chemotactic factors (chemokines) in the maternal uterus and the sensitivity of circulating leukocytes for migrating towards these chemokines. In PTL, IL1β, an apex cytokine that is produced in response to sterile/infectious inducers of PTL, stimulates the expression of chemokines in the maternal uterus. A recent collaborative study between Olson and Chemtob labs showed that an inhibitor of the IL1 receptor, rytvela, prevents IL1β-induced PTL in mice. We hypothesize that a mouse that delivers preterm due to IL1β-treatment demonstrates leukocyte invasion due to increased uterine chemokines and enhanced leukocyte activity, and that these effects are prevented with rytvela.

Methods. 33 pregnant CD1 mice were used in this study. PTL was induced by intrauterine administration of IL1β (3µg) at gestational day (GD)16, and mice were monitored every 30min until delivery and euthanization (n=7). Rytvela (1mg/Kg/12h) was subcutaneously administered in IL1β-treated (n=5) and non-treated mice (n=5). These rytvela-treated, sham control (n=6), and non-treated (n=5) mice were euthanized at GD17. Non-treated mice were also euthanized at GD18.5 (n=5). Uterine chemokines were extracted from mouse lower uterus, normalized to wet tissue weight, and compared by the relative migration of human leukocytes towards these chemokines. Mouse leukocytes were isolated from whole blood via erythrocyte sedimentation and compared by using RT-qPCR to measure their mRNA abundance for cytokines (IL1β, IL6, TNFα, CCL2). Mouse leukocytes were also compared by their relative migration towards a standard chemokine. Statistical analysis was performed by one-way ANOVA.

Results. 85% of mice delivered preterm within 24h of IL1β-administration; none delivered preterm when pre-treated with rytvela. Uterine chemokines at GD18.5 stimulated more migration of human leukocytes than at GD17 ($p<0.05$), and uterine chemokines from PTL-induced mice stimulated similar migration as those from non-treated mice. mRNA abundance for IL1β, IL6, TNFα and CCL2 was 5-10x greater in mouse leukocytes at GD18.5 than GD17 ($p<0.05$), and 4-8x greater for PTL-induced mice than controls ($p<0.05$). Mouse leukocyte migration towards a standard chemokine was approximately 10% greater in PTL-induced mice than controls ($p<0.01$, $p<0.05$). Rytvela reversed the effects of IL1β-administration.

Conclusions. This is the first work that establishes IL1β as an inducer of leukocyte invasion in mice by enhancing leukocyte chemotaxis. This work also demonstrates that rytvela can successfully antagonize the effects of IL1β in the mouse.

Funded By: WCHRI Trainee Travel Grant; CIHR; Bauld Family Scholarship

Abstract #: 38
Presenter: Ronan Noble
Supervisor: Stephane Bourque
Title: Perinatal iron deficiency causes no overt blood pressure changes in neonatal offspring
Authors: Ronan Noble, Andrew Woodman, Sareh Panahi, Ferrante Gragasin, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Epidemiological and animal studies on the developmental origins of health and disease (DOHaD) have shown susceptibility to non-communicable chronic diseases may be traced to stressors during pregnancy. Our group investigates the outcomes of maternal iron-deficiency (ID), the most common nutritional deficiency worldwide. An estimated 23% of Canadian women become iron-deficient during pregnancy; in the developing world this number climbs as high as 50-80%. Perinatal ID offspring have been shown to develop hypertension with associated risks evident as early as childhood. Currently the mechanisms by which ID causes hypertension are poorly understood, though hypertension is often characterized by a reduction in nitric oxide (NO) bioavailability. We hypothesize prenatal ID leads to a reduction in NO and vasodilatory capacity, coupled with an increase in vasoconstrictor response and hypertension.

Methods: Sprague Dawley rats were fed either an iron replete (control), or an iron-restricted diet 2 weeks prior to and throughout the pregnancy. After birth all dams were fed an iron replete diet. Offspring were weighed on postnatal day (PD) 0 within 12 hours of birth. Separate offspring were anaesthetized and instrumented with indwelling arterial catheters on PD7, 14, and 21. Vascular function was assessed in vivo with the intravenous administration of: the endothelium-dependent vasodilator methacholine (MCh), the NO-donor sodium nitroprusside (SNP), and the alpha-adrenergic agonist phenylephrine (PE). Hemodynamic responses to these agents were assessed in the absence and presence of NO synthase inhibitor L-NAME. Offspring were euthanized following vascular function experiments and Hb were collected.

Results: Maternal iron restriction resulted in a 31% decrease in maternal hemoglobin, and a 55% and 21% reduction in PD1 offspring Hb and bodyweight respectively when compared to controls. Mean arterial pressure (MAP) increased continuously with age from PD7 through PD21, although no differences between perinatal ID and control offspring were observed at any time point. ID did not alter the vascular response of either MCh or SNP, either in the absence or presence of L-NAME. Female ID offspring showed a reduced hemodynamic response to PE on PD7, which normalized, and was no longer evident on PD14 and PD21. In contrast, male offspring exhibited an enhanced response to PE on PD14, which was longer evident by PD21.

Conclusion: These results suggest perinatal ID does not cause alterations in neonatal baseline blood pressure regulation. However, perinatal ID is associated with altered vasoconstrictor responses to PE, and this effect is both time and sex-dependent.

Funded By: WCHRI Innovation Grant; CIHR

Abstract #: 39
Presenter: Andrew Woodman
Supervisor: Stephane Bourque
Title: Perinatal iron-deficiency combined with a high-salt diet causes sex-dependent vascular dysfunction in adult offspring
Authors: Andrew Woodman, Ronan Noble, Sareh Panahi, Ferrante Gragasin, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Background

Susceptibility to chronic disease in later life can be 'programmed' by stressors during pregnancy, such as iron deficiency (ID) – the most common nutritional deficiency worldwide. Offspring born from ID mothers develop hypertension and exhibit impaired renal salt handling, to which a reduction in the bioavailability of endogenous vasodilator nitric oxide (NO) may contribute. We hypothesized perinatal ID causes hypertension, reduced NO bioavailability, and vascular dysfunction. Furthermore, we hypothesized that these effects would be exacerbated in the presence of a high-salt diet – a common known cardiovascular stress.

Methods

Sprague Dawley rats were fed either an iron-replete (CTL) or low-iron diet (ID) two weeks prior to and throughout pregnancy. Upon giving birth, all dams and offspring were fed an iron-replete diet. Six weeks prior to experimentation, a subgroup of ID and CTL offspring were allocated to normal-salt (NS; 0.27% w/w) or high-salt diets (HS; 5% NaCl w/w). At 6 months of age, offspring were anesthetized and instrumented with indwelling arterial catheters for hemodynamic assessments, and isolated mesenteric artery function was assessed via wire myography. Vascular function was assessed with: (i) endothelium-dependent vasodilator methacholine, (ii) NO donor sodium nitroprusside (SNP), and (iii) adrenergic agonist phenylephrine (PE; all in the presence or absence of nitric oxide synthase inhibitor L-NAME).

Results

ID resulted in a 34% decrease in maternal hemoglobin (Hb) and a 52% decrease in offspring Hb at birth with respect to controls. Male offspring exhibit increased systolic blood pressure (SBP) due to both ID and HS (both $P<0.05$). Changes in blood pressure from administration of L-NAME (i.e. systemic NO signalling) were decreased in male offspring due to both ID and HS (both $P<0.05$). Female SBP is unaffected by either ID or HS, albeit NO signalling was reduced by HS ($P<0.05$). EC_{50} for methacholine in male offspring was increased by HS ($P=0.05$), whereas in females HS increased methacholine EC_{50} in CTL ($P<0.01$) but not ID offspring ($P_{int}=0.007$). In the absence of endogenous NO production male, but not female, offspring exhibit decreased EC_{50} for phenylephrine due to ID ($P=0.03$). Changes in EC_{50} for MCh due to L-NAME were enhanced in male CTL ($P<0.05$) but not ID offspring due to HS ($P_{int}=0.03$), whereas NO contributions in females remained unchanged. Differences in reactivity to SNP were not observed.

Conclusions

Perinatal ID causes sex-specific programming of vascular dysfunction in adult offspring. Reduced NO signalling and endothelial dysfunction is implicated in altering systemic blood pressure and vascular responses, predominantly in males.

Funded By: WCHRI Innovation Grant; CIHR; Alberta Innovates

Abstract #: 40
Presenter: Victoria L. Meah
Supervisor: Margie H. Davenport
Title: The impact of prenatal exercise on neonatal and childhood outcomes: a systematic review and meta-analysis
Authors: Victoria L. Meah, Stephanie-May Ruchat, Gregory A. Davies, Rachel Skow, Nick Barrowman, Kristi B. Adamo, Veronica J Poitras, Casey E. Gray, Alejandra Jaramillo Garcia, Frances Sobierajski, Laurel Riske, Marina James, Amariah J. Kathol, Megan Nuspl, Andree-Anne Marchand, Taniya S. Nagpal, Linda Slater, Ashley Weeks, Ruben Barakat, Michelle F. Mottola, Margie H. Davenport.
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

INTRODUCTION

Neonatal complications during pregnancy, such as preterm birth and growth restriction, are associated with both short- and long-term health issues for the child. Despite having many known benefits for the mother, prenatal exercise has previously been suggested to potentially increase the risk of such neonatal complications; however, the impact remains poorly understood. The purpose of this review was to evaluate the effect of prenatal exercise on neonatal and childhood health outcomes, and to establish whether a dose-response relationship existed between frequency, intensity, and volume of maternal exercise and the outcomes of interest.

METHODS

A systematic review with random effects meta-analysis and meta-regression was conducted as part of a series of reviews that form the evidence base for the *2018 Canadian Guidelines for Physical Activity throughout Pregnancy*. Online databases were searched up to January 5, 2017. Studies of all designs were eligible (except case studies) if published in English, Spanish or French, and contained information on the relevant Population (pregnant women without contraindication to exercise), Intervention (subjective/objective measures of frequency, intensity, duration, volume or type of exercise), Comparator (no exercise or different frequency, intensity, duration, volume or type of exercise) and Outcomes (preterm birth, gestational age, birthweight, small for gestational age [<2500g; <10th percentile], large for gestational age [>4000g; >90th percentile], intrauterine growth restriction, neonatal hypoglycaemia, metabolic acidosis [cord blood pH, base excess], hyperbilirubinemia, APGAR scores, NICU admittance, shoulder dystocia, brachial plexus injury, neonatal body composition [percent body fat, body weight, body mass index {BMI}, ponderal index] childhood obesity [percent body fat, body weight, BMI] and developmental milestones [including cognitive, psychosocial, motor skills]).

RESULTS

A total of 135 studies (N=166,094) were included. There was "high" quality evidence from exercise-only randomized controlled trials (RCTs) showing a 39% reduction in the odds of having a baby >4,000g (macrosomia; 15 RCTs, n=3,670; OR 0.61, 95% CI 0.41, 0.92) in women who exercised compared to women who did not exercise, without affecting the odds of growth-restricted, preterm or low birthweight babies. There were no significant associations between prenatal exercise and any remaining neonatal or childhood outcomes. Finally, there was no dose-response relationship between prenatal exercise and any outcome of interest.

CONCLUSIONS

Prenatal exercise reduces the odds of macrosomia and is not associated with neonatal complications or adverse childhood outcomes. Prenatal exercise does not place undue risk on the developing baby and may benefit long-term health through avoidance of excessive fetal growth.

Funded By: CIHR, Heart & Stroke Foundation, Fonds de recherche du Québec

Abstract #: 41
Presenter: MIchael Sullivan
Supervisor: Winnie Sia
Title: Reducing excessive laboratory investigations for preeclampsia: A quality improvement project
Authors: Michael Sullivan, Xavier Thompson, Pam Mathura, Alex Wong, Jennifer Crawford, Claudia Salguero, Jonathan Tankel, Venu Jain, Winnie Sia
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Objectives: Pregnant women suspected of having preeclampsia receive laboratory workup for diagnosis and surveillance. However, many investigations are ordered from past protocols currently deemed inappropriate- with considerable healthcare cost and the potential for iatrogenic harm. This quality improvement (QI) project aimed to reduce unnecessary patient blood draws and healthcare costs.

Methods: Quality improvement tools were used to identify current process strengths and gaps in the preeclampsia workup process on the labour and delivery, triage, and antepartum wards of a tertiary care centre. Healthcare providers were surveyed regarding laboratory ordering practices to identify problems, which was corroborated with 20 inpatient chart reviews. Laboratory usage and costs were analyzed pre-intervention (Jan-April 2017) and post-intervention (Sept 2017-April 2018). An algorithm for ordering preeclampsia investigations was developed by a multidisciplinary team, consisting of obstetrics, obstetrical medicine, maternal-fetal medicine and biochemistry. The algorithm was posted on wards, and pocket aide distributed to residents. Practitioners, residents and nurses were invited to educational seminars to support adoption and posters raised awareness of the issue. Post-intervention surveys and chart reviews were conducted, and interventions refined.

Results: Pre-intervention survey data indicated most providers ordered broad panels of investigations, rarely re-evaluated investigation frequency, and were unaware of laboratory costs. A majority of respondents acknowledged that some investigations did not affect patient management and based these decisions on institutional convention. Baseline data showed 10,462 investigations were ordered ($69,350) (Jan-April, 2017). Post-intervention data (Sept 2017- April 2018) revealed a 39% reduction in investigation cost ($6851/month), particularly those of low clinical utility including D-dimer (69%) and urea (71%). Investigations such as ALT and creatinine, which were recommended in the algorithm, had consistent rates of utilization pre- and post-intervention. This indicates that investigations were ordered at a similar frequency, with judicious ordering practices accounting for overall cost savings. Weekly data show the post-intervention reduction in excessive laboratory investigations were sustained and stable.

Conclusions: This simple and inexpensive intervention reduced overall laboratory investigations for preeclampsia, particularly those of low clinical utility. This resulted in annualized savings of $89060 (39%). However, institutional ordering conventions are a significant barrier to change and some providers are resistant. We will sustain change with continued practitioner and nursing education, and aim to disseminate the algorithm as part of a Choosing Wisely Canada preeclampsia toolkit.

Funded By: Integrated Quality Management

Abstract #: 42
Presenter: Rebecca Clark
Supervisor: Yan Yuan
Title: Risk prediction for nonsurgical premature menopause in childhood cancer survivors
Authors: Rebecca Clark, Yan Yuan
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Female childhood cancer survivors are at an increased risk of developing nonsurgical premature menopause (NSPM) due to toxicities from their treatment. NSPM occurs when ovarian function is retained for at least 5 years after diagnosis but menopause develops naturally before age 40, which can negatively impact quality of life and reduce potential reproductive years. Risk factors include an older age at diagnosis and treatment with high doses of chemotherapy and radiation. In order to help physicians, patients and their families have informed discussions of the need for fertility preservation interventions, we aimed to develop prediction algorithms to estimate the risk of patients developing NSPM.

Methods

Data was acquired for 5,508 female participants of the Childhood Cancer Survivor Study. Candidate models were developed on a training set of 4,054 observations using the time-specific logistic regression model with competing risks (TLR-CR), the Fine-Gray regression model (FGR) and the random survival forest method with competing risks (RSF-CR). Model performance and accuracy were measured using the time-specific area under the ROC curve (AUC_t), the time-specific average positive predictive value (AP_t) and calibration curves on both the training set and a test set of 1,454 observations for internal validation.

Results

Following model development, predictors included minimum ovarian radiation dose, cumulative chemotherapy exposure, bone marrow transplant and age at diagnosis. The TLR-CR, FGR and RSF-CR models performed similarly during model evaluation on the training set. At 15 years post diagnosis, they produced AUC_t values between 0.76-0.78, and AP_t values larger than the event rate of 1.72% (AP_t = 6-7%) indicating adequate model performance. The estimated AUC_t values decreased when internal validation was conducted (AUC_t = 0.59-0.69). All AP_t values remained larger than the event rate of 2.51% (AP_t = 8-11%), and the ratio between AP_t and the event rate increased for the RSF-CR and TLR-CR models. AUC_t and AP_t values from the test set over 10-20 years post diagnosis showed similar findings. The models were well calibrated on both datasets, especially for low risk patients.

Conclusions

Obtaining risk estimates for NSPM has the potential to improve the lives of childhood cancer survivors. Overall, the TLR-CR model performed consistently with good calibration from the training to test set, and was the best model of the three. Moving forward, generalizability will be assessed through validation on an external cohort.

Funded By: WCHRI Graduate Studentship; Trainee Travel Grant; CIHR

Abstract #: 43
Presenter: Dhruvesh Patel
Supervisor: Catherine Field
Title: Feeding a bioactive oil enriched in stearidonic acid is beneficial for immune system maturation in young rat pups.
Authors: Dhruvesh Patel, Susan Goruk, Caroline Richard, Marnie Newell, Guanqun Chen, Catherine Field
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Low dietary intake of n-3 long chain (LC) polyunsaturated fatty acids (PUFA) early in life is associated with risk of atopic diseases. The objective of this study was to determine the immunomodulatory effects of feeding a bioactive oil enriched in stearidonic acid (SDA), as a source of n-3 LCPUFA during suckling and weaning on immune system maturation.

Methods: Pregnant rats (dams) were randomized to consume a nutritionally complete diet with or without SDA (3% or 0% SDA w/w total fat) and at weaning their pups were fed the same diets for 3 weeks. Differences in bodyweight, immune cell phenotypes, lipid composition, and *ex-vivo* cytokine response to lipopolysaccharide challenge (LPS, a bacterial component) were measured in dams and offspring at the end of suckling (3wk) and weaning (6wk) period.

Results: Pups fed SDA diet (6wks) had 7% higher bodyweight than control pups ($p<0.02$). At 3wks, pups from dams fed SDA diet had higher plasma n-3 LCPUFA level, including docosahexaenoic acid (DHA) which was 30% higher than control ($p<0.05$). Similarly, pups fed SDA diet at 6wks had higher plasma n-3 LCPUFA levels, specifically eicosapentaenoic acid (EPA) ($p<0.05$) with no differences in arachidonic acid (ARA), an n-6 LCPUFA. Consistently, pups from SDA group had a higher incorporation of EPA and thus resulted in a lower total n-6/n-3 ratio in the phospholipids of immune cells. Moreover, pups fed SDA diet had 23% higher proportion of splenocytes that were T helper (T_h) cells (CD3+CD4+) and these T_h cells had a higher expression of co-stimulatory molecule (CD28) ($p<0.02$) and these T_h cells are more representative of a more mature phenotype. Similarly, at 6wks pups weaned to the SDA diet had higher proportion of T_h cells with 30% higher expression of an activation marker (CD25, an IL-2 receptor) ($p<0.001$). Splenocytes challenged *ex-vivo* with LPS showed significantly lower production of Th1 inflammatory cytokines (IL-6 and TNF-α) but higher production of Th2 non-inflammatory cytokines (IL-10; $p<0.01$). This switch in the balance of Th1/Th2 cytokines together with a more mature T cell phenotype is a marker of maturation of immune system and important for the development of food tolerance.

Conclusion: Feeding a diet enriched in SDA, an 18-carbon long n-3 PUFA, provided a precursor for the biosynthesis of essential n-3 LCPUFA (EPA and DHA) and supported early stage immune system maturation.

Funded By: Phytola, Alberta Canola Producers Commission and NSERC

Abstract #: 44
Presenter: Paula Ospina Lopez
Supervisor: Margaret McNeely
Title: Exploring physical rehabilitation referral and service provision for children and adolescents with cancer across Canada
Authors: Paula Ospina Lopez, Lesley Wiart, David Eisenstat, Margaret McNeely
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives

Children undergoing cancer treatment are at high risk of developing serious long-term effects. Physical rehabilitation may reduce the burden of cancer side effects; however, few children report accessing physical rehabilitation services. This study aims to explore the frequency and reasons for referrals, as well as barriers and facilitators to pediatric oncology rehabilitation.

Methods/Approach

A national cross-sectional web-based survey in English and French languages was conducted. Participants identified were Canadian healthcare professionals who provide and/or refer children and adolescents with cancer to physical rehabilitation services.The survey included questions on referral patterns including numbers of children with cancer either seen or referred in the respective facility per year, use of protocols and clinical-practice guidelines, and current barriers and facilitators that impact the provision of physical rehabilitation programs for children and adolescents with cancer.

Results/Findings

A total of 54 responses were received including physical therapists (n= 27), nurse and nurse practitioners (n= 10), pediatric oncologists and oncology residents (n= 9), occupational therapists (n= 6), a speech-language pathologist (n= 1), and an exercise professional (n= 1). Findings suggest low referral rates of children and adolescents with cancer to physical rehabilitation services. Few healthcare professionals reported using physical rehabilitation protocols or guidelines in practice. Barriers to service provision included a lack of funding/ resources and healthcare professionals with expertise in pediatric oncology rehabilitation.

Conclusions

Main findings of the survey suggest (1) low rates of referral to physical rehabilitation services, (2) lack of funding and resources for physical rehabilitation services, and (3) the need for healthcare professionals with expertise specific to pediatric oncology rehabilitation within hospitals and community settings. There is high interest from oncology healthcare professionals to develop and support the implementation of clinical practice guidelines in physical rehabilitation for childhood cancer survivors.

Funded By:

Abstract #: 45
Presenter: Anne Halpin
Supervisor: Lori West
Title: Modernizing ABO antibody detection: Bead-based assays to characterize ABO antibodies
Authors: Anne Halpin, Janet Zhou, Jean Pearcey, Todd L. Lowary, Christopher W. Cairo, Gour Daskhan, Bruce Motyka, Stephanie Maier, Lori J. West
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Children waiting for heart transplantation face high wait list mortality due, in part, to low numbers of size and ABO-compatible heart donors. ABO-incompatible (ABOi) transplantation increases the donor pool for these patients and can be safely performed in infants as they have not yet started producing ABO antibodies (ABO-Ab). Accurate characterization of ABO-Ab is critical to assess their impact in ABOi transplantation as well as the risk of rejection, especially as children age on the wait list. The current ABO-Ab detection erythrocyte agglutination method is limited by lack of ABO-subtype specificity, difficulty in ABO-Ab isotype differentiation, and poor reproducibility. We previously developed a slide micro-array (SAMA) method for ABO-Ab analysis to address these limitations. Our aim was to develop a similar bead-based solid phase assay.

Methods: ABO A-subtype antigens (I,II,III,IV,V,VI) were coupled to Luminex beads and quantified using monoclonal ABO-Ab. Bovine serum albumin and alpha-Gal antigen were coupled as negative/positive controls, respectively. IgG and IgM isotypes with specificities for ABO A-subtypes were measured and compared (n=39 healthy donors) by mean fluorescence intensity (MFI). Bead *vs*SAMA results were also compared. Wilcoxon signed-rank test was used to compare differences between methods.

Results: ABO A antigens were detected on the beads using monoclonal antibodies. Variation in ABO-A-Ab levels to ABO A-subtypes was detected in the healthy donors. By bead detection, IgG and IgM antibodies showed no significant difference in paired data. IgG and IgM ABO-Ab were clearly detectable in all non-ABO A controls. ABO B controls had similar IgM ABO-A-Ab levels to ABO O controls but lower levels of IgG. ABO-Ab were detected at higher MFI in the bead vs SAMA method for many subtypes.

Conclusion: This method successfully measures ABO-A-Ab and shows promise for clinical laboratory implementation, where bead-based assays are already used. The specificity of this assay will facilitate assessment of ABO-Ab to subtypes, which are known to be expressed differently in cardiac endothelium than on erythrocytes, creating potential for red cell-based methods to yield false positive results. The ability to measure both IgM and IgG ABO antibodies makes it possible to evaluate of the role of each isotype in transplantation; isotype ABO-Ab differentiation may be particularly relevant in the setting of plasmapheresis, which more efficiently removes IgM antibodies. Routine measurement of ABO-Ab by this method would provide more a more clinically-relevant assessment of risk of cardiac rejection and may lead to a larger window of safe ABOi transplantation.

Funded By: Heart & Stroke Foundation; GycoNet

Abstract #: 46
Presenter: Alexa Thompson
Supervisor: Joel Dacks
Title: Bioinformatic analysis of a malarial invasion protein demonstrates Apicomplexan parasite specificity
Authors: Alexa Thompson, Zeinab Ebrahimzadeh, Angana Mukherjee, David Gaumond, Marie-Ève Crochetière, Audrey Sergerie, Dominic Gagnon, Joel Dacks, Dave Richard
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Title: Bioinformatic analysis of a malarial invasion protein demonstrates Apicomplexan parasite specificity

Introduction: Nearly half the world's population is at risk for malarial infections with pregnant women and children being the most vulnerable to the disease. In 2016, 445,000 malaria deaths were reported by WHO. Malaria is predominantly caused by *Plasmodium falciparum*, a parasite that is transmitted through mosquito vectors. Once bitten, the parasite travels to and multiplies in the liver before invading red blood cells, where the parasite continues it growth before eventually killing the red blood cells and releasing daughter parasites. The invasion process into red blood cells harbors a phosphoinositide-binding protein we call PfPH2, which is involved in exocytosis of invasion-related micronemes. With the knowledge that most Apicomplexan parasites harbor micronemes, we performed a bioinformatic analysis of PfPH2 in an attempt to identify this process in other infectious parasites.

Methods: Homology searching of PfPH2 was performed using BLASTp and HMMer into the protein databases of select Apicomplexans and their outgroups. Candidate orthologues were considered positive when both the forward and reverse BLAST searches generated an E-value below a 0.05 threshold, when the top reverse BLAST hit was PfPH2, and when the order of magnitude between hits was 2 or higher. The conserved PH domain from PfPH2 was removed in the query for BLASTp to mitigate the possibility of false positives. The modified query was also used to generate the HMMer profile for HMMer searches. Identified orthologues were aligned and run through Phyre2.0 to identify any shared domain structures and sequence motifs.

Results: Positive orthologues for PfPH2 were identified in all Apicomplexans selected. No orthologues were identified in the Chromerid outgroup to the Apicomplexa, nor in other Alveolates. Alignments of all hits identified conserved PH and SMN_C superfamily domains at the N-terminal regions of the proteins. A closer analysis of the amino acids within the PH domain demonstrated partial conservation of the $KX_n(K/R)XR$ phosphoinositide-binding sequence motif between orthologues.

Conclusions: Orthologues of the *P.falciparum* PfPH2 protein are specific to the Apicomplexan phylum, indicating the protein was most likely gained during evolution as an adaption to parasitism. The protein's specificity to parasites suggests that the invasion mechanism used by *P.falciparum* is likely also used by other parasites. Based on partial conservation of the phosphoinositide-binding motif, it's probable parasites secrete micronemes in a similar manner as the malarial parasite does; by means of binding PIP residues to facilitate the invasion process.

Funded By: CIHR; Discovery Grant from the Natural Sciences and Engineering Research Council of Canada

Abstract #: 47
Presenter: Geraldine Huynh
Supervisor: Hien Huynh
Title: Infliximab dose to level study In patients with pediatric Crohn's disease
Authors: Geraldine Huynh, Matthew W. Carroll , Anne M. Griffiths , Wael El-Matary , Connie Prosser , Jennifer deBruyn, Diane Mould , Alexandra Petrova, Eytan Wine, Hien Huynh
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives: Infliximab (IFX) is shown to be well-tolerated and effective for induction and maintenance of remission in Crohn's disease (CD). The main objective of this prospective observational study was to evaluate the relationship between IFX serum levels during induction therapy and short-term clinical outcome in children with CD

Methods: Conducted at the Stollery Children's Hospital, Hospital for Sick Children, and Manitoba Children's Hospital, baseline data were collected including disease classification (Paris classification) and clinical activity [Weighted Pediatric Crohn's Disease Activity index (wPCDAI)]. The induction IFX dose was prescribed by the treating physician ranging from 5mg-10mg/kg. Dose adjustments and time between infusions were optimized by the physician based on patient clinical response, laboratory results and previous drug trough levels. Up to a total of 8 IFX levels per patient were collected: trough and peak levels at the IFX infusions #2 and #4 (Visit 3 and 4), trough levels at Visits 5, 6 and 7, and trough level at Visit 8 (prior to IFX infusion #5). 3 antibodies to infliximab (ATI) levels, fecal calprotectin, wPCDAI, CBC diff, liver function tests, albumin, ESR and CRP were also collected at each infusion.

Results: 35 patients were recruited and followed for up to 22 weeks over 8 study visits. 81.3% went into clinical remission by infusion 5. Median dose for IFX infusion 1 was 6.0 mg/kg (IQR: 5.0-7.0) and increased to 7.0mg/kg (IQR: 5.0-8.25) for infusion 5. Trough and peak levels were not statistically correlated with clinical remission at all time points except for the trough level at infusion 5 with lower levels for patients in clinical remission (p=0.036). ATI drawn at baseline, infusion 4 and infusion 5 were all negative. 80% of patients were dose optimized and did not follow the standard infusion regimen of week 0, 2,6 and 14 weeks. Based on therapeutic drug monitoring, dose 4 had the most variability in infusion frequencies, but the median dose frequency was shortened to Q6W. Shorter infusion interval prior to infusion 4 was associated with higher wPCDAI at infusion 3 ($r = -0.403$, $p = 0.016$). Increase in IFX dose at infusion 4 was associated with lower IFX trough level at infusion 3 ($r = -0.373$, $p = 0.03$). There was also a positive correlation between IFX clearance and FCP at dose 1 ($p = 0.026$), ESR at dose 1 ($p = 0.047$) and 5 ($p = 0.044$) and wPCDAI at dose 4 ($p = 0.027$) and frequency at dose 4 ($p = 0.001$).

Conclusion: There was no statistical difference between trough levels. However, most patients were dose optimized and went into clinical remission by infusion 5. ATI levels were negative and all patients had detectable IFX levels, which suggests that early dose adjustment may reduce the risk of ATI formation.

Funded By: WCHRI Innovation Grant; A David and Beatrice Reidford Research Scholarship

Abstract #: 48
Presenter: Kevin Yoon
Supervisor: Andrew Waskiewicz
Title: Manipulation of key eye dorsoventral axis patterning genes, vax2 and tbx2b, affects the closure of a novel optic fissure
Authors: Kevin H. Yoon, Jennifer C. Hocking, Ordan Lehmann, Andrew J. Waskiewicz
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Congenital ocular coloboma is a genetic disorder that is typically observed as a cleft formation in the inferior aspect of the eye due to the failure of the choroid fissure to close during eye development. Recently, identification of individuals with coloboma in the superior aspect of the iris led to the discovery of a novel fissure, referred to as the superior ocular sulcus (SOS), that is transiently present on the dorsal aspect of the optic cup during early zebrafish eye development. We aim to elucidate the role of dorsoventral axis patterning genes identified in patient-derived exome sequencing data, *VAX2* and *TBX2*, in the closure of SOS.

Methods: To assess the roles of these genes in SOS closure during eye development, we have begun studying *vax2*, *tbx2a*, and *tbx2b* using zebrafish. Zebrafish with the null mutant allele, *tbx2b*^{fby}, was studied to investigate the effects of *tbx2b* loss in SOS closure. Additionally, CRISPR-Cas9 mutagenesis was used to create a knockout model for *vax2* in zebrafish. Furthermore, mRNA constructs have been created to study the consequences of *vax2* overexpression and the physiological consequences of the variant found in the patient.

Results: Investigation of differences in dorsal eye morphology between wildtype and *tbx2b* mutant embryos suggests that loss of *tbx2b* results in delayed SOS closure. To elucidate the effects of *vax2* loss in SOS formation and closure using zebrafish, we have successfully created a null allele, *vax2*^{ua1017}, resulting in deletion of 83 base-pairs upstream of the homeodomain region, which in turn produces a truncated protein. However, *vax2*$^{ua1017/ua1017}$ homozygous embryos display no signs of SOS closure defects. Conversely, overexpression of wildtype *VAX2* mRNA in wildtype zebrafish embryos leads to a delay in SOS closure, with the SOS being observable up to 50 hpf, in a dosage-dependent manner. This effect is slightly exacerbated in embryos injected with *VAX2* mRNA containing the patient-derived variant sequence. Overexpression of *VAX2* also leads to perturbation of DV axis patterning gene expression, including that of *tbx5a* and *tbx2b*.

Conclusions: Our findings suggest that overexpression of *vax2*, a Shh-induced regulator of Wnt signaling in the ventral eye, can lead to delay in SOS closure. Conversely, we have found that decrease in *tbx2b* expression results in SOS closure delay. In addition, we will study the effects of *TBX2* overexpression in zebrafish eye development. Our initial results provide support for a model in which DV eye patterning is essential for SOS closure.

Funded By: WCHRI Innovation Grant; CIHR; Alberta Innovates; NSERC

Abstract #: 49
Presenter: Babak Nami
Supervisor: Zhixiang Wang
Title: Comprehensive genetic and expression profiling of tubulin gene superfamily in breast cancer and its relation to taxane resistance
Authors: Babak Nami, Zhixiang Wang
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Objective

Taxanes are a class of chemotherapeutic agents that inhibit cell division by disrupting mitotic spindle through the stabilization of microtubule. Most of breast cancers (BC) tumors show resistance against taxanes partially due to alterations in tubulin genes. In this project we investigated tubulin isoforms in BC to explore any correlation between tubulin alterations and taxane resistance.

Approach

Genetic alteration and expression profiling of 28 tubulin isoforms in 6,714 BC tumor samples from 4,205 BC cases were analyzed. Protein-protein, drug-protein and alterations neighbor genes in tubulin pathways were examined in the tumor samples. To study correlation between promoter activity and expression of the tubulin isoforms in BC, we analyzed the ChIP-seq enrichment of active promoter histone mark H3K4me3 and mRNA expression profile of MCF-7, ZR-75-30, SKBR-3 and MDA-MB-231 cell lines. Potential correlation between tubulin alterations and taxane resistance, were investigated by studying the expression profile of taxane-sensitive and resistant BC tumors also the MDA-MB-231 cells acquired resistance to paclitaxel. All genomic data were obtained from public databases.

Results

Results showed that TUBD1 and TUBB3 were the most frequently amplified and deleted tubulin genes in the BC tumors respectively. The interaction analysis showed physical interactions of α-, β- and γ-tubulin isoforms with each other. The most of FDA-approved tubulin inhibitor drugs including taxanes target only β-tubulins but not other isoforms. The analysis also revealed sex tubulin-interacting neighbor proteins including ENCCT3, NEK2, PFDN2, PTP4A3, SDCCAG8 and TBCE which were altered in at least 20% of the tumors. Expression of tubulin genes in BC cell lines were correlated with H3K4me3 enrichment of their promoter chromatin. Analyzing expression profile of BC tumors and tumor-adjacent normal breast tissues showed upregulation of TUBA1A, TUBA1C, TUBB and TUBB3 and downregulation of TUBB2A, TUBB2B, TUBB6, TUBB7P pseudogene, and TUBGCP2 in the tumor tissues compared to the normal breast tissues. Analyzing taxane-sensitive versus taxane-resistant tumors revealed that expression of TUBB3 and TUBB6 was significantly downregulated in the taxane-resistant tumors.

Conclusions

Our results suggest that downregulation of tumor TUBB3 and TUBB6 is correlated with taxane resistance in BC. Therefore, we suggest that lower tumor TUBB3 and TUBB6 expression may be used as a predictive marker for taxane resistance. We also propose that mutations of α- and γ-tubulin isoforms also may cause taxane-resistance by gaining β-tubulin-like function to bypass taxane action. Thus, studying the molecular pathology of α- and γ-tubulin mutations is needed for future direction.

Funded By: WCHRI Graduate Studentship

Abstract #: 50
Presenter: Rutuja Kadam
Supervisor: Peter Metcalfe
Title: Bladder outlet obstruction mediated EMT is inhibited by mesenchymal stem cells
Authors: Rutuja Kadam, Jennifer Carleton, Bridget Wiafe, Peter Metcalfe
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Partial bladder outlet obstruction (pBOO) results in significant stress on the bladder and is associated with significant morbidity. The increased pressure generated by the detrusor muscle, required to empty the bladder, results in: tissue hypoxia, mechanical stretch, smooth muscle cell hypertrophy, and, eventually, tissue fibrosis. Recent work by our lab has demonstrated that this progression can be inhibited by mesenchymal stem cell (MSC) therapy. Epithelial Mesenchymal Transition (EMT) is a biologic process which converts epithelial cells to motile mesenchymal cells. Type 2 EMT, in chronic inflammation, is associated abnormal myofibroblast formation which leads to derangement of the extracellular matrix and tissue fibrosis. We hypothesize that the pathophysiology secondary to pBOO is secondary to EMT and inhibition of this is the mechanism by which MSC achieve their potent therapeutic effects.

Methods

pBOO was surgically induced in female Sprague-Dawley rats which were simultaneously treated with MSC. Both 2 and 4 weeks after obstruction, protein markers for EMT were visualized in pBOO treated and pBOO-, non-treated bladders via immunohistochemistry and Trichrome staining. These results were correlated with urodynamic measures of bladder function.

Results

After pBOO, αSMA was localized in the suburothelial layer. Vimentin and collagen were localized in the lamina propria and muscle layer. Our results show that these proteins were downregulated in the treatment groups. Additionally, urodynamic measures show that high pressure generated by pBOO decreased in treatment groups.

Conclusion

This data confirms the role of EMT after pBOO, and confirms its inhibition after MSC treatment. This is likely due to inhibition of the inflammatory cascade. Further work is ongoing to determine if EMT can be reversed with a delayed treatment model. Thus, we have provided further insight into the pathophysiology of pBOO and believe this will aid in the progression to clinical trials and ultimately, improve patient care.

Funded By: WH Lakey Summer Studentship Award

Abstract #: 51
Presenter: Kara Goodkey
Supervisor: Toshifumi Yokota
Title: In-vivo comparison of antisense oligonucleotide treatment for spinal muscular atrophy
Authors: Kara Goodkey, Tejal Aslesh, Aleksander Touznik, Rika Maruyama, Toshifumi Yokota
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Spinal muscular atrophy (SMA) is an incurable autosomal recessive disorder, affecting nerve cells in the spinal cord and weakening voluntary muscles, caused by a loss of function mutation in the *survival motor neuron 1* (*SMN1*) gene. SMA is one of the most common genetic causes of infant death. *SMN2* is a paralogue of *SMN1* but is unable to produce adequate amounts of the protein due to skipping of *exon 7* caused by a single nucleotide transition of C to T in exon 7. The intronic splicing silencer number 1 (ISS-N1) in *SMN2* intron 7 acts on the C to T transition removing exon 7 from the mRNA. As a consequence, 90% of SMN2 pre-mRNAs are truncated and non-functional. A recently approved treatment for SMA uses an antisense oligonucleotide (AON), a short DNA-like molecule, targeting *SMN2*. A modified 2'-O-methoxyethyl (MOE) AON called nusinersen (Spinraza) hybridizes to the ISS-N1 in *SMN2* and blocks the excision of exon 7. The FDA approved nusinersen for treatment of SMA in 2016;however, the high cost of the drug and invasive intrathecal treatment create the need for a safer and less expensive method of treatment. We comparedthree AON chemistries as a treatment for SMA; MOE, locked nucleic acid/DNA mixmers (LNA/DNA), and phosphorodiamidate morpholino oligomers (PMO).

Methods

Neonatal SMA mouse pups carrying the human *SMN2* transgene were injected subcutaneously (SC) or intracerebroventricularly (ICV) with one of the three chemistries of AONs on postnatal day 0 (P0) and sacrificed at P7. Quantitative RT-PCR was used to test for full length expression of the *SMN2* gene in four different tissues extracted from each pup. This data coupled with functional tests and survival curves highlighted the efficacy of each chemistry as a treatment.

Results

SC and ICV injections with LNA/DNA significantly increased the expression of full-length SMN2 but did not extend the survival of SMA mice. In contrast, PMO treatment increased full-length expression of the *SMN2* gene and extended the survival time of SMA mice equivalent to the approved MOE therapy that is currently on the market.

Conclusions

This study makes the PMO chemistry a more promising candidate than LNA/DNA for future AON therapies for SMA patients.

Funded By: WCHRI Innovation Grant; CIHR, Friends of Garret Cummin Research Funds, HM Toupin Neurological Science Research Funds, Slipchuck SMA Research Foundation

Abstract #: 52
Presenter: Dyanna Melo
Supervisor: Toshifumi Yokota
Title: Minimized PMO cocktails efficiently skip exons 45-55: A treatment for Duchenne muscular dystrophy (DMD)
Authors: Dyanna Melo, Kenji Rowel. Q Lim, Toshifumi Yokota
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder mostly caused by out-of-frame mutations in the DMD gene. DMD is the most common lethal genetic disorder affecting approximately 1 in 5000 male births. Children experience muscle weakness, progressing to the loss of ambulation at a young age, followed by cardiomyopathy and respiratory failure, which are the leading causes of death. There is currently no cure for DMD. One of the most promising therapeutic tools for DMD is exon skipping using antisense oligonucleotides (AONs), which changes out-of-frame mutations to in-frame deletions as seen in milder Becker muscular dystrophy (BMD). The first AON treatment called eteplirsen was approved by the FDA in 2016; however eteplirsen faces many challenges including limited applicability (up to 14% of DMD patients), poor uptake and low efficacy.

Methods

To combat these challenges, we sought to skip exons 45-55 using AONs which would be applicable to ~47% of DMD patients. The resulting protein after treatment would likely be more functional than that produced by eteplirsen, as this specific deletion is associated with an exceptionally mild phenotype and sometimes found in asymptomatic individuals, likely due to a stable and functional protein structure. To improve the cellular uptake and efficacy, we employed next-generation AONs called cell-penetrating peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs). Our lab has previously shown that 12 PMOs (unmodified) can be used to skip exons 45-55; however, 12 PMOs are expensive, may be redundant and require rigorous testing for approval. Here we explore using a minimized cocktail to induce exon 45-55 skipping. Various minimized cocktails were tested by transfecting AONs into immortalized human patient muscle cells and evaluating the skipping efficacy by RT-PCR and protein expression by Western blotting. The cocktails were also tested via injections into humanized DMD transgenic mice carrying a human DMD sequence in vivo.

Results

We found that minimized cocktails containing 3-6 AONs produced ~20-60% exon 45-55 skipping and that PPMOs increased skipping efficiency by ~60% compared to PMOs.

Conclusion

Minimized cocktails produced efficient exon 45-55 skipping and are promising to restore functional dystrophin levels and ameliorate the DMD phenotype. A minimized PPMO cocktail is a promising treatment for DMD. In the future, further minimizations will be explored, the peptide-conjugate will be applied and the cocktails will be tested in cell/animal models with different mutations.

Funded By: WCHRI Summer Studentship; Alberta Innovates

Abstract #: 53
Presenter: Chantal Yoon
Supervisor: Toshifumi Yokota
Title: Restoration of dystrophin using CRISPR/Cas9 in a dog model of Duchenne muscular dystrophy with a mutation in N-terminal mutation hotspot
Authors: Rika Maruyama, Aleksander Touznik, Quynh Nguyen
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder prevalent in one in 5000 males. DMD causes progressive muscle weakness, degeneration, ultimately resulting in respiratory or cardiac failure. DMD is caused by a mutation in the DMD gene which encodes for dystrophin, a structural protein that protects the muscle membrane. Frameshift or point mutations leading to a premature stop codon in the DMD gene prevent dystrophin production. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-technology can excise mutations by guiding the Cas9 endonuclease to specific locations on DNA using single guide RNAs (gRNAs), producing two double-stranded breaks and creating an in-frame deletion of one or more exons by non-homologous end-joining (NHEJ) to restore the expression of truncated, but partially functional, dystrophin protein as seen in milder Becker muscular dystrophy (BMD). Our study sought to restore the dystrophin reading frame using CRISPR vectors in primary dystrophic dog muscle cells (myotubes).

Methods

We employed two strategies, exons 3-9 skipping and exons 6-9 skipping. Although exons 6-9 and 3-9 deletions are both associated with BMD, we and other groups identified that the exons 3-9 deletion is associated with a remarkably mild phenotype. We tested the efficacy of single guide RNA (gRNA) combinations in skipping targeted exons in the canine DMD gene. After transfecting the gRNAs, we carried out T7 Endonuclease1 (T7E1) assay to confirm the CRISPR/Cas9 genome editing activity. We employed RT-PCR to confirm the in-frame dystrophin expression in treated cells.

Results

T7E1 assay confirmed genomic DNA editing at all the targeted sites. Genomic PCR and RT-PCR demonstrated that genome-editing using these guide RNAs and SaCas9 led to efficient exons 3-9 and 6-9 skipping, encompassing a region of 118 kb and 152 kb, respectively. After transfection into dystrophic dog cells, in-frame dystrophin was restored to levels ranging 10-24% of normal levels, as confirmed by RT-PCR.

Conclusion

CRISPR/Cas9-mediated genome editing led to potentially therapeutic levels of dystrophin expression in dystrophic dog muscle cells in vitro. These findings suggest great potential for genome editing approaches for the treatment of DMD.

Funded By:

Abstract #: 54
Presenter: Kerry Wong
Supervisor: Joan Robinson
Title: Characterizing RSV hospitalizations in Alberta: a retrospective database analysis
Authors: Kerry Wong, Michael Hawkes
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Bronchiolitis is the leading cause for hospital admissions in infants and toddlers. Most commonly, it is caused by respiratory syncytial virus (RSV). Most children will be infected with RSV by the age of 2 years, typically developing a mild respiratory disease. However, risk factors such as congenital heart disease predispose children to more severe disease requiring hospital admission. Passive immunization with palivizumab is available to high-risk children. The Canadian Pediatric Society does not recommend continuing prophylaxis for a child who develops breakthrough bronchiolitis given the low risk of repeat RSV hospitalization in one season. However, in Alberta, palivizumab is sometimes continued despite a breakthrough hospitalization. The objectives of this project is to describe the epidemiology of RSV hospitalizations in Alberta and determine how many children are readmitted for RSV infection within one RSV season. By characterizing patients who are readmitted, we can better determine who may benefit from continuing palivizumab.

Methods

We performed a retrospective database analysis. Using a discharge database search strategy validated at the Children's Hospital of Eastern Ontario (CHEO) we searched the Alberta Health Services Discharge Abstract Database for pediatric patients less than 5 years old admitted to any hospital in Alberta with a primary diagnosis of RSV from July 1, 2004 until June 30, 2017. We also searched for cases in which a patient had a repeat admission with RSV as their primary diagnosis a minimum of 30 days after the first admission (to identify new versus prolonged infections).

Results

From July 1, 2004 – June 30, 2017, 10 212 unique patients were admitted with RSV in Alberta, with a total of 10 967 admissions. Of these, 4504 (44%) were female. The median age was 5.4 months (interquartile range 1.9-14.5); 89% of patients were under 2 years old. 666 (6.5%) patients were re-admitted for RSV at least once during the study period. 454/666 (68%) of second admissions occurred within 30 days of the initial hospital discharge. There were 39 cases (0.38%) in which RSV re-admission occurred during the same season, but more than 30 days after the first hospitalization of that season. Children admitted multiple times are more likely to have bronchopulmonary dysplasia, congenital heart disease, trisomy 21, been previously intubated, and previously admitted to PICU, compared to patients with only one RSV admission.

Conclusions

Although RSV hospitalization is common, repeat hospitalizations for RSV in one season are rare.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant

Abstract #: 55
Presenter: Alexandra Rydz
Supervisor: Mercedes Chan
Title: Quality of referral letters to pediatric rheumatology and its impact on access to care
Authors: Alexandra Rydz, Fangfang Fu, Mark Drew, Dax Rumsey, Yan Yuan, Mercedes Chan
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Delays in access to care in pediatric rheumatology (PR) are well known and may lead to significant morbidity. Barriers to accessing PR care are multifactorial, with the literature suggesting that incomplete referral letters contribute to delays in subspecialist assessment. This study is the first to describe the content of referral letters to PR at a tertiary care pediatric center, the impact of incomplete referral letters on time to PR assessment, and the proportion of referrals that resulted in a rheumatic diagnosis

Methods: All new referral letters to PR at our centre over a 22-month period were prospectively evaluated by attending pediatric rheumatologists on a weekly basis during patient triage using a referrals' checklist. Letters were reviewed for eight components of a high-quality referral: rheumatologic diagnosis of concern; patient symptoms; investigations; physical examination (musculoskeletal and general); co-morbidities; current and past management; and medications. Referrals for patients >17 years old were excluded. Basic patient demographics and referring physician specialty were also collected.

Dates of triage decisions and resultant PR appointments were recorded, and times to PR appointments calculated. Where incomplete referrals required additional information from referring physicians, we calculated the subsequent delays in time to triage. Final diagnoses made by rheumatologists were recorded retrospectively. Descriptive statistics were applied to the data.

Results: Referrals (n=447) were received and analyzed from: family doctors 45.2%, pediatric providers (including subspecialists) 42.1%, and others (e.g., pediatric ENT) 12.8%. The frequency of specific components included in referral letters were: patient symptoms (94%); investigations (68.7%); diagnosis of concern (54.6%); musculoskeletal examination (47.7%); medications (43%); current and past management (41.4%); co-morbidities (40.3%); and general examination (27.5%).

Further information was requested from 63/447 referrals (14.1%) regarding one or more of: pertinent history (57/63, 90.5%), physical examination (57/63, 90.5%), rheumatologic diagnosis of concern (44/63, 69.8%), or investigations (29/63, 46.0%). Where missing information was requested, the median delay in triage time was 1.0 week (IQR 0.1 to 2.0).

Overall, -200/447 referrals (44.7%) resulted in rheumatic diagnosis. -More referrals from pediatric providers resulted in rheumatic diagnosis than referrals from family physicians (50.5% vs 40.1%, p = 0.049).

Conclusions: Pertinent history and physical examination are the most commonly omitted components of referral letters to PR. Requesting missing information delayed triage. Only approximately half of PR referrals resulted in a PR diagnosis. These findings can inform medical education initiatives to facilitate access to timely PR care.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant; Canadian Initiative for Outcomes in Rheumatology Care

Abstract #: 56
Presenter: Kristen Hui
Supervisor: Yarden Yanishevsky
Title: Rate and management of anaphylaxis across three Canadian pediatrics emergency departments
Authors: Kristen Hui, Aaron Van der Leek , Moshe Ben-Shoshan, Maryna Yaskina, Yarden Yanishevsky
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction:

The incidence of anaphylaxis in the industrial world is reportedly increasing, but Canadian pediatrics data is limited to two studies, both of which report an incidence relatively high compared to the rest of Europe and North America. Our primary objective is to compare the rate, triggers and management of anaphylaxis between three Canadian pediatric emergency departments (ED). Secondary objectives are to describe our center's compliance to national guidelines on discharge planning.

Methods:

We conducted a retrospective chart review of patients seen at Stollery Children's Hospital (SCH) ED, a tertiary care centre in Edmonton from March 2011 to February 2012. Those meeting criteria based on the Second Symposium on the Definition of Anaphylaxis were included. As part of the Cross-Canada Anaphylaxis Registry (C-CARE), patient demographics, atopic comorbidities, triggers, symptoms and management were collected. Anaphylaxis severity was classified according to a three-grade-scale. The results were compared to the Montreal Children's Hospital (MCH) and British Columbia Children's Hospital (BCCH) C-CARE data by comparing 95% confidence intervals. Binomial logistic regression was performed to identify factors associated with in-hospital epinephrine use.

Results:

Of 30,687 ED visits at the SCH, 101 visits were for anaphylaxis (0.33%, [95% CI, 0.27%, 0.40%]), similar to rates reported by the BCCH (0.37% [0.33%, 0.41%]) and MCCH (0.38% [0.35%, 0.41%]). Across all three sites, food triggers accounted for approximately 80% of cases, and anaphylaxis of moderate severity accounted for approximately 70%. SCH had a higher percentage of pre-hospital administration for epinephrine, antihistamines and steroids use (38.6% [29.7%, 48.7%], 61.4% [52.5%, 71.5%] and 8.9% [5.0%, 14.8%] respectively) compared to BCCH (27.7% [23.2%, 32.8%], 50.6%, [45.2%, 56.0%] and 0.6% [0.1%, 2.33%] respectively) and MCH (33.1% [29.5%, 37.0%], 47.1 [43.1%, 51.0%] and 1.1% [0.5%, 2.4%] respectively). Epinephrine use overall was similar at SCH, BCCH and MCH (76.2% [68.3%, 84.3%], 81.8% [77.2%, 85.6%] and 69.5% [65.7, 73.1%] respectively). At each site less than 3% of cases required admission. Epinephrine use in the ED was less likely if epinephrine was administered prior to arrival in ED and more likely in severe cases. Upon discharge from the SCH, 79% of patients had a prescription for epinephrine, and 50% were referred to or already had an allergist.

Conclusion:

Our study represents a diverse patient population allowing a more broad application to the improve pediatric anaphylaxis management, with an emphasis on increased epinephrine use inside and outside of the ED.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant

Abstract #: 57
Presenter: George Slim
Supervisor: Justine Turner
Title: A novel GLP-2 analogue improves both functional and structural adaptation, including intestinal linear growth, in neonatal piglets without ileum
Authors: George Slim, Marihan Lansing, Pamela Wizzard, Patrick Nation, Paul Wales, Justine Turner
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Objectives: Glucagon-like peptide-2 (GLP-2) is a trophic hormone released from ileal L-cells. There is current interest in the use of GLP-2 analogues to treat short bowel syndrome (SBS) and enable independence from parenteral nutrition (PN). We have previously shown in neonatal piglets, that ileal resection restricts intestinal adaptation and decreases endogenous GLP-2 production. Continuous treatment with intravenous (iv) native recombinant GLP-2 enhanced adaptation and reduced days on PN, yet no significant growth in intestinal length was detected. Neonates have unique potential for intestinal growth, an unmet therapeutic goal of new therapies. In this study, we examined a novel long-acting subcutaneous (sc) GLP-2 analogue, FE203799 (FE), for efficacy in promoting linear intestinal growth, nutrient absorption and adaptation.

Methods: 2-5 days old neonatal piglets were randomized to saline control (n=9) versus FE treatment (n=8). All piglets underwent 75% intestinal resection with total ileal resection and jejunocolic anastomosis. PN was provided at 100% requirements, with trophic enteral nutrition given at 20% of requirements. Saline or FE treatment were administered days 0 and 4 at 5mg/kg/dose (sc). Terminal laparotomy was performed on postoperative day 7, small intestinal length and weight were measured, and tissue was collected for jejunal histology. Data was analyzed by parametric Student t-test's (P<0.05) and presented as mean ± SD.

Results: Both FE and saline treated piglets had gained equivalent weight by day 7 (3.70 ±0.32 kg vs 3.47±0.22; P=0.10). FE treated piglets had greater growth in intestinal length (+12.8±8.1 vs -6.1±7.6 cm; P<0.001), higher small intestinal wet weight (29.4±4.5 vs 22.7±1.8 gm; P=0.001) and longer villus height (0.86±0.17 vs 0.66±0.13 mm; P=0.015) when compared to saline treated piglets. FE treated piglets had lower measured loss of total energy (1735 vs 2199 j/g; p=0.034) and fat (22.8 vs 30.2 mg/g; p=0.055); while fecal loss of carbohydrate (10.0 vs 19.5 mg/g) and nitrogen (2.4 vs 2.6 mg/g; p=0.56) were not different compared to saline.

Conclusions: The novel GLP-2 analogue, FE203799, improved both histological intestinal adaptation and linear intestinal growth in a neonatal model of SBS with complete loss of ileum. As opposed to our prior experience with iv GLP-2, intestinal lengthening is a notable outcome of particular relevance to the growing neonates, which may improve clinical long-term response. Moreover, given its long half-life (30 hours), this GLP-2 analogue can be administered once or twice weekly, which is superior to administration as daily SC injections or continuous IV therapy, especially for children.

Funded By: GlyPharma Therapeutic

Abstract #: 58
Presenter: L. Cynthia Gunaratnam
Supervisor: Joan Robinson
Title: Biomarkers for diagnosis of bacterial pneumonia in children with respiratory distress
Authors: L. Cynthia Gunaratnam, Joan Robinson, Michael Hawkes
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Pneumonia is a significant cause of morbidity and mortality in children worldwide, especially those in resource-poor settings. Diagnosis of pneumonia is currently primarily clinical, making it difficult to differentiate from other causes of respiratory distress. Adjunctive tests are available but vary in sensitivity and specificity, and are difficult to access in resource-limited settings. Of note, differentiating bacterial from viral pneumonia is unreliable using current clinical guidelines and adjunctive tests. This differentiation is an important one to promote timely antibiotic initiation for bacterial cases and simultaneous prevention of antibiotic overuse and resistance. As a result, there is increasing interest in identifying novel biomarkers that diagnose bacterial pneumonia with greater specificity.

Objective: To perform a systematic review assessing the ability of biomarkers to correctly identify bacterial pneumonia in children (birth to 18 years old) who present with respiratory distress.

Methods: Electronic Databases MEDLINE, EMBASE, CENTRAL, and Global Health were searched. Search was not restricted to any languages. Grey literature search was restricted to ClinicalTrials.gov, WHOICTRP, and any within reference lists of articles. Selection criteria: i) diagnostic research studies of biomarkers in children with respiratory distress, ii) bacterial pneumonia must have been a separate outcome, iii) atypical bacterial pneumonia could be separated or included within bacterial pneumonia, and iv) studies involving adults must have separated out pediatric results. Inception and validation studies were included but biomarkers being validated required cut-off values.

Results: The search yielded 1812 studies (duplicates removed) which were screened independently by two investigators with 92% agreement. Disagreements were reviewed and 115 articles were agreed upon and will be reviewed in full. Identified biomarkers were many including CRP, lipocalin-2, haptoglobin, prealbumin, and vWF.

Conclusion: This review will provide a list of biomarkers studied to date in pediatric pneumonias and their success or lack thereof in differentiating bacterial versus other etiologies. Validation studies are expected to reveal potential cut-off values for individual or combinations of biomarkers which may allow future studies to be more cohesively designed.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant; SPOR (Strategy for Patient-Oriented Research)

women & children's health research institute

Abstract #: 59
Presenter: Maikel Farhan
Supervisor: Todd Alexander
Title: The role of Claudin 12 in renal tubular ion transport
Authors: Maikel Farhan, Todd Alexander
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Hypercalciuria is the excretion of urine with too much calcium (Ca^{2+}). It is the major risk factor for kidney stones and is also associated with osteoporosis. Two thirds of Ca is reabsorbed from the renal proximal tubule via a paracellular mechanism, which is not well understood at the molecular level. A group of proteins, designated claudins, mediate paracellular, i.e. between cells, ion transport. Claudin 12 (CLDN12) has been implicated in paracellular Ca^{2+} flux across the intestine where it participates in Vit D-dependent Ca^{2+} absorption. CLDN12 is expressed in the kidney however, its role there is unknown. We aim therefore to elucidate the role of CLDN12 in kidney paracellular ion transport.

Methods: Three month old wild-type (WT), or Claudin-12 deficient (CLDN12 KO) mice were placed in metabolic cages for three days with free access to normal chow and water. Urine was collected every 24 hrs for electrolytes analysis via ion chromatography. Blood was collected on day 3 for analysis of serum creatinine via High-performance liquid chromatography. Data from a cohort of at least 12 mice per group was used to generate the results.

Results: Previous work from the Alexander laboratory found no difference in serum electrolytes between WT and CLDN12 KO mice. Similarly, there was no difference in chow eaten, water drank, urine output or weight between genotypes. The current data shows that both groups had the same kidney filtration capacity as indicated by the 24 hrs creatinine excretion and creatinine clearance rate. Additionally, there was no difference in chloride, phosphorus, calcium, sodium, magnesium, or potassium excretion in urine. Importantly, a gender based subgroup analysis also did not reveal a significant difference in ions excretion.

Conclusion: Although, ex vivo studies have found that CLDN12 alters proximal tubule Ca^{2+} permeability, there was no change in urinary Ca^{2+} excretion of CLDN12 KO mice. Further, CLDN12 deficiency did not alter other ion excretion or the glomerular filtration rate. These results suggest a compensatory paracellular or transcellular mechanism that regulates Ca^{2+} transport. This research aims to understand renal tubular physiology, which will help to develop novel diagnostic tools and treatments for common disorders such as kidney stones, and osteoporosis.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant

Abstract #: 60
Presenter: Noureen Ali
Supervisor: Sujata Persad
Title: Active-beta-catenin (ABC) as a prognostic marker for osteosarcoma progression
Authors: Noureen Ali, Elizabeth Garcia, Takaaki Landry, Hunter McColl, Consolato Sergi, David Eisenstat
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Osteosarcoma (OS) is an aggressive primary bone malignancy having peak incidence in children and young adolescents. Outcome remains poor for most patients with metastatic disease which develops in 1 of every 5 cases. Presently, there are no widely recommended screening tests for early diagnosis of OS and no reliable prognostic marker for aggressive/metastatic disease. We investigated the putative role of the Wnt/β-catenin pathway, specifically the transcriptionally active form of β-catenin, Active-Beta-Catenin (ABC), in OS progression.

Methods: We used two pairs of cell lines that simulate OS progression: Saos2/Saos2-LM7 and HOS/HOS-143B. MMP2 and MMP9 activity were used to confirm the greater metastatic potential of Saos2-LM7 & HOS-143B compared to SaOS2 and HOS respectively. Total cellular/nuclear levels/localization of ABC/β-catenin were evaluated by Western blot, immunofluorescence (IF) and High Content analysis. Transcriptional activity of ABC/β-catenin was evaluated by qRT-PCR of target genes (MMP2, MMP9, Cyclin D1 and VEGFA). For immunohistochemical analysis of nuclear ABC levels in OS tissue samples, we used an OS tumor tissue array (TMA) which comprised of 40 primary OS samples and included information on tumor stage, age and sex of patients (colon cancer tissue-positive control; spleen-negative control). ABC immunoreactivity was scored based on percentage of nuclear ABC staining throughout the tumor tissue. The TMA results were further analyzed via statistical tests.

Results: Results show significantly higher cellular levels of ABC in the SaOS2-LM7 and HOS-143B cell lines compared to the respective parent cell lines (SaOS2 & HOS). Additionally, ABC exhibited a more prominent nuclear localization in SaOS2-LM7 and HOS-143B cell lines compared to SaOS2 & HOS, respectively. No significant differences in cellular levels and localization of β-catenin were observed. SaOS2-LM7/HOS-143B exhibited significantly greater transcriptional activity. TMA results show that 34 out of 40 tumor cores (85%) exhibited positive nuclear staining for ABC. Association between sex and nuclear ABC staining was tested via Fisher's exact test and the results showed no significant association ($p=0.64$). We also found that patients with positive nuclear ABC staining were, on average, younger (mean age = 28.91 years) than patients with negative nuclear ABC staining (mean age = 44.67 years).

Conclusion: The strong correlation between cellular/nuclear ABC levels/activity and OS progression supports the potential for ABC to serve as a prognostic marker for OS progression.

Funded By: WCHRI Trainee Travel Grant; Hair Massacure

Abstract #: 61
Presenter: Nicholas Ruel
Supervisor: James Hammond
Title: Two splice variants of SLC43A3 both encode nucleobase transporters that mediate 6-mercaptopurine uptake and cytotoxic activity.
Authors: Khanh Hoa Nguyen
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: 6-mercaptopurine (6-MP) is a nucleobase analog used in the treatment of ulcerative colitis, Crohn's disease, and particularly paediatric acute lymphoblastic leukemia (ALL). The use of 6-MP is associated with severe side effects, including hepatotoxicity and myelosuppression. These side effects can result in discontinuation of therapy and subsequent disease relapse. SLC43A3, an orphan member of the amino acid transporter gene family, was recently found to encode the protein Equilibrative Nucleobase Transporter 1 (ENBT1) which can transport purine nucleobases such as adenine and hypoxanthine. There are two splice variants of SLC43A3 (SLC43A3_1 and SLC43A3_2) that encode proteins that differ by 13 amino acids in the first predicted extracellular loop of the protein. We have shown that ENBT1.1, encoded by SLC43A3_1, can mediate the uptake of 6-MP. However, ENBT1.2 (encoded by SLC43A3_2) has not been studied. We hypothesize that ENBT1.1 and ENBT1.2 differ in their 6-MP transport characteristics.

Methods: HEK293 cells, which express low quantities of ENBT1, were stably transfected with myc-tagged SLC43A3_1 and SLC43A3_2. [^{3}H]Adenine and [^{14}C]6-MP were used to assess ENBT1 function and its sensitivity to inhibitors. MTT was used to assess the effect of ENBT1 expression on the cytotoxicity of 6-MP. The impact of ENBT1 expression on the levels of other putative transporters and enzymes implicated in 6-MP action was assessed by qPCR.

Results: ENBT1.1 and ENBT1.2 both transported adenine and 6-MP with similar K_m values (ENBT1.1 - Adenine: 37 ± 13µM, 6-MP: 163 ± 63µM; ENBT1.2 - Adenine: 40 ± 13µM, 6-MP: 188 ± 34µM). Both isoforms also had similar affinities for a variety of competing substrates and inhibitors. Furthermore, 6-MP cytotoxicity was increased significantly in both SLC43A3_1-transfected (7-fold; Log EC_{50} = -6.05 ± 0.11) and SLC43A3_2-transfected cells (11-fold; Log EC_{50} = -6.29 ± 0.03) relative to un-transfected HEK293 cells (Log EC_{50} = -5.25 ± 0.08). Transfection of HEK293 cells with SLC43A3_1 and SLC43A3_2 lead to decreases in the transcripts for SLC29A2, ABCC4, and ABCC5, suggesting cross-regulatory mechanisms in the expression of other transporters associated with nucleobase handling by these cells.

Conclusions: ENBT1.1 and ENBT1.2 transport both adenine and 6-MP. Both isoforms handle 6-MP in a similar fashion and the expression of either isoform enhances 6-MP cytotoxicity. This supports the null hypothesis, and indicates that both variants of SLC43A3 contribute to 6-MP uptake and differences in the expression of either variant may impact 6-MP therapy in ALL.

Funded By: The Cancer Research Society

Abstract #: 62
Presenter: Andrew Mackie
Supervisor:
Title: The Fontan Education Study
Authors: Andrew Mackie, Kathryn Rankin, Sunjidatul Islam, Leanne Meakins, Elina Williams, Mary Bauman, Patti Massicotte, Gwen Rempel
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: The Fontan operation is performed at 2-4 years of age and is the final surgical intervention needed in children with a univentricular heart. Prior work by our team identified that parent's perspectives of major challenges post Fontan include a) psychological distress, b) prolonged pleural drainage resulting in lengthy hospitalizations, and c) the need for postoperative anticoagulation. The aim of this study was to develop and evaluate a video-based online teaching program for parents to address these challenges.

Methods: We conducted a cluster randomized controlled trial at the Stollery Children's Hospital, comparing an educational intervention vs. control. The educational intervention consisted of three brief (~5 minute) professionally-developed whiteboard videos, available to parents online from the time of enrolment in the preadmission clinic to 1 month postoperatively. Each video addressed one of the unique post- Fontan challenges described above. Content of videos was created by a parent with lived experience and team members. The primary outcome was the parent's State Trait Anxiety Inventory (STAI)-State score 1-week post-surgery. Secondary endpoints were a) parent STAI-State score 1-month postoperatively, b) the child's Post Hospital Behaviour Questionnaire (PHBQ) score 1 week and 1 month postoperatively (a measure of resilience, i.e. the capacity to cope with stress), and c) parent feedback on the videos.

Results: We enrolled 26 children and their families, 16 into the intervention group. Mean (SD) STAI-State score 1 week postoperatively was 52.8 (6.5) vs. 55.5 (3.9) in the intervention and control groups respectively (p=0.25). One month postoperatively, mean (SD) STAI-State score was 50.9 (6.7) vs. 53.9 (3.9) respectively (p=0.25). PHBQ scores did not differ between study groups. Preoperatively, 71% of parents agreed or strongly agreed that the video about psychological distress was helpful, compared to 100% of parents 1-month postoperatively. Parents agreed or strongly agreed that the video on prolonged pleural drainage was helpful preoperatively (79%) and 1 month postoperatively (89%). Prior to surgery parents agreed or strongly agreed (86%) that the video on postoperative anticoagulation was helpful compared to 89% 1-month postoperatively.

Conclusions: An online video-based intervention program did not impact STAI-State scores or PHBQ scores. However, the majority of parents agreed that the videos were helpful, particularly when their child was 1-month post-surgery. Qualitative data from semi-structured interviews is needed to identify how and why parents found this intervention helpful, in order to inform future educational video development for parents of children undergoing cardiac surgery.

Funded By: WCHRI PaCET Award

Abstract #: 63
Presenter: Andrej Roczkowsky
Supervisor: Richard Schulz
Title: Junctophilin-2: a putative target of MMP-2 in myocardial ischemia-reperfusion injury
Authors: Andrej Roczkowsky, Brandon Chan, Tim Lee, Richard Schulz
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Within cardiomyocytes, voltage gated Ca^{2+} channels in t-tubules are arranged in close propinquity to ryanodine receptors in the sarcoplasmic reticulum to allow coordinated Ca^{2+} induced-Ca^{2+} release. Junctophilin-2 is a structural membrane protein which tethers the t-tubule to the sarcoplasmic reticulum. Junctophilin-2 proteolysis is implicated in both in vivo and ex vivo models of ischemia-reperfusion (IR) injury. However, calpains were suggested as the protease responsible for this as calpain inhibitors, which are also potent matrix metalloproteinase-2 (MMP-2) inhibitors, were used. Matrix metalloproteinase-2 (MMP-2) is a Zn^{2+} dependent protease which becomes activated during IR injury, impairing cardiac contractile function by cleaving specific intracellular proteins during IR injury. As MMP-2 and junctophilin-2 are enriched along the Z-disc and sarcoplasmic reticulum in cardiac myocytes, we hypothesized that MMP-2 contributes to contractile dysfunction in IR injury by cleaving junctophilin-2.

Methods

Isolated rat hearts were perfused in working mode aerobically or subjected to global, no-flow ischemia followed by reperfusion in the presence and absence of the selective MMP inhibitor ARP-100 (10 µM, n=6-7/group). Following perfusion, hearts were flash frozen, homogenized, ventricular extracts were prepared. To detect interactions between MMP-2 and junctophilin-2, MMP-2 was immunoprecipitated from extracts and then probed for junctophilin-2 by immunoblot. To test the susceptibility of junctophilin-2 to proteolysis, ventricular extracts were incubated with MMP-2 for 2 hr at 37°C. Immunoblot was performed on ventricular extracts to assess levels of junctophilin-2 and its major degradation products in the three groups.

Results

In hearts subjected to IR injury, ARP-100 significantly improved contractile function at the end of reperfusion from 2.6±1.0 to 5.1±0.5 $mmHg \cdot mL \cdot min^{-1} \cdot 10^{-3}$ in IR versus IR+ARP-100 groups, respectively ($p<0.05$). Full length junctophilin-2 and its degradation product were detected in both aerobic and I/R hearts. MMP-2 cleaved junctophilin-2 in ventricular extracts in a concentration-dependent manner. Junctophilin-2 in vitro proteolysis was MMP-dependent as it was prevented by ARP-100. No differences in junctophilin-2 levels were observed between aerobic, IR, and IR+ARP-100 groups. However, the level of cleaved junctophilin-2 (≈75 kDa) was significantly increased in IR relative to aerobic hearts ($p<0.05$) and this band was lowered in the IR+ARP-100 group.

Conclusions

Inhibition of MMP-2 is protective in myocardial IR injury. We show for the first time that junctophilin-2 proteolysis in IR injury is prevented by MMP inhibitors. The results of this study provide insight to the mechanisms of IR injury and may aid in the development of MMP inhibitors to treat ischemic heart disease.

Funded By: Canadian Institutes of Health Research

Abstract #: 64
Presenter: Stephanie Perrin
Supervisor: Simon Urschel
Title: Developing a graphic novel for medical education of teenage heart transplant patients
Authors: Stephanie Perrin
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Teenagers have the highest rate of rejection and organ failure among all patients receiving organ transplants. This is vastly associated to behavioral challenges and non-adherence to medical therapy and to date no successful strategies for improvement have been found. The aim of this project was to develop a new tool to educate and motivate teenage heart transplant patients to take increased ownership of their long-term health.

Methods/Approach

We hypothesized that a graphic novel—an age-appropriate, visually appealing medium that employs visual communication and storytelling—would help accomplish this purpose.We started with a pilot group of transplanted teenagers, parents, and health care providers who were interviewed about what aspects of life post-transplant they felt needed to be addressed by the graphic novel. The responses of the pilot group—as well as in-progress feedback—were used to guide the direction, style, and content of the novel. A detailed script was then developed and edited. Finally the pages were designed and inked using realistic pen-and-ink drawing techniques.

Results

Interviews revealed that parents and health care providers had different ideas about what aspects would be valuable to address. They also revealed that the primary tensions faced by the teenagers were not necessarily related to the post-transplant lifestyle, but rather to typical teenage concerns, specifically conflict with parents. We determined that the graphic novel would be the most effective if it addressed transplant guidelines subtly and indirectly so as to avoid typical teenage mental blocks against instructional texts and conversations. We developed an adventurous and humorous storyline—involving mutant worms, chickens, Edmonton in the future, and characters who had had heart transplants—that the teenagers would find appealing, while slipping in relevant messages pointed out as key concerns by the pilot group, such as the need for increased fluid consumption. The illustrations are not yet fully completed. Once the graphic novel is complete, it will be printed and 30 teenage patients will evaluate the quality, appeal, and motivational efficacy of the graphic novel using standardized questionnaires.

Conclusions

This is a first attempt at using a graphic novel to specifically reach and motivate transplanted teenagers. Our interviews have revealed that a subtle approach will be more likely to succeed and accordingly have used storytelling as a means to transport messages without triggering oppositional reflexes. The larger scale evaluation will reveal whether or not this approach is a meaningful strategy for teenage health education.

Funded By: Undergraduate Research Initiate Stipend

women & children's health research institute

Abstract #: 65
Presenter: Sofia Sagaidak
Supervisor: Rhonda Rosychuk
Title: Emergency department crowding and outcomes for children presenting for asthma in Alberta, Canada
Authors: Sofia Sagaidak, Brian H Rowe, Rhonda J Rosychuk
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Emergency department (ED) crowding is a major problem in the Canadian healthcare system. Asthma is one of the most common chronic conditions in children and severe acute exacerbations require prompt and appropriate care in the ED. In Canada, limited evidence exists regarding the impacts of ED crowding on outcomes for patients with acute asthma.

Hypothesis: ED crowding negatively affects patient outcomes.

Methods: Population-based retrospective cohort study using administrative health data analyzing all ED visits for asthma made by children aged 2-17 in 18 high-volume EDs in Alberta from fiscal years 2010-2014. Two ED crowding metrics were calculated: time to physician initial assessment (PIA) and length of stay (LOS) and the association on patient outcomes was determined with univariable and multivariable models. Outcomes assessed include patient PIA, ED LOS, disposition status, time to ED return, times to first physician follow-up (e.g., primary vs. specialist care), time from disposition decision to admission, and hospital LOS.

Results: There were 25,388 presentations for asthma. The mean of the median PIA and ED LOS crowding metrics were 1h 33m and 3h 52m, respectively and remained stable over time. Higher crowding metrics were associated with increased individual patient PIA and ED LOS, patients more likely to be transferred or leave without completion of care, discharged patients less likely to return to the ED after discharge, and patient delays in admission. There were few deaths in the ED or after the ED presentation.

Conclusion: The median ED crowding metrics influenced patient outcomes during the ED presentation and did not show evidence of associations with longer-term outcomes. Further study is required to determine the best crowding metric to assess any associations for important long-term outcomes.

Funded By: WCHRI Summer Studentship; Alberta Innovates

Abstract #: 66
Presenter: Robin Manaloor
Supervisor: Samina Ali
Title: Humanoid robot-based distraction to reduce pain and distress during venipuncture in the pediatric emergency department: A randomized clinical trial
Authors: Robin Manaloor, Lisa Hartling, Keon Ma, Mithra Sivakumar, Tanya Beran, Shannon Scott, Leanne Sigismund, Timothy Graham, Sarah Curtis, Samina Ali
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Intravenous insertion (IVI) is identified by children as extremely painful and the resultant distress can have lasting negative consequences. There is an urgent need to better manage such procedures.

Objective(s): To compare pain and distress with the addition of humanoid robot-based distraction to standard of care, versus standard of care alone, in children undergoing IVI. We hypothesized that the addition of humanoid robot-based distraction would decrease pain and distress.

Design/Methods: This two-armed randomized controlled trial (RCT) was operated from April 2017 to May 2018 at the Stollery Children's Hospital emergency department (ED). Due to the nature of the intervention, it was not possible to blind participants, research assistants, or ED staff. The biostatistician assessing the primary objective was blind to treatment allocation.

Participants: Children aged 6 to 11 years, requiring IVI were included. Exclusion criteria included hearing or visual impairments, neurocognitive delays, sensory impairment to pain, previous enrollment, and discretion of the ED clinical staff. 426 pediatric patients were screened and 340 were excluded.

Results: We recruited 86 children of which 55% (47/86) were male; 9% (7/82) were premature at birth; 82% (67/82) had a previous ED visit; 30% (25/82) required previous hospitalization; and 78% (64/82) had previous IV placement. Median age was 9 years with no other significant differences between groups at baseline. A clinical reduction in pain of one face and a statistically significant reduction in distress was observed with the addition of humanoid robot-based distraction to standard care. The Faces Pain Score (FPS-R) during the IV procedure was 4 in the standard care group alone, compared to 2 with the addition of humanoid robot-based distraction (T=0.13). The total distress score during the procedure measured via the Observational Scale of Behavioral Distress (OSBD-R) was 1.49±2.36 (standard of care) compared to 0.78±1.32 (robot group) (P=0.047). Change in parental state anxiety pre-procedure versus immediately after the procedure was not significantly different between groups (P=0.49). Parental satisfaction with the IV start was 93% (39/42) for the robot distraction arm compared to 74% (29/39) in the standard care arm (P=0.03). Parents were also more satisfied with management of their child's pain in the robot group (95% very satisfied) compared with standard care (72% very satisfied) (P=0.002).

Conclusions: Humanoid robot-based distraction therapy appears to have a positive impact on pain and distress in children undergoing IVI. Further trials need to be completed to confirm utility in other settings and age groups.

Funded By: WCHRI Start-up or Retention Funding

Abstract #: 67
Presenter: Catalina Garcia-Hidalgo
Supervisor: Georg Schmölzer
Title: 18% vs. 21% vs. 100% oxygen during chest compression during sustained inflation cardiopulmonary resuscitation in asphyxiated newborn piglets
Authors: Catalina Garcia-Hidalgo, Anne Lee Solevåg, Po-Yin Cheung, Tze-Fun Lee, Megan O'Reilly, Georg Schmölzer
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Current resuscitation guidelines recommend 100% oxygen (O_2) at the onset of chest compressions. However the most effective percentage of oxygen during chestcompressions remains unknown.

Objectives

To determine if 18% or 21% O_2 is as effective as 100% O_2 to achieve return of spontaneous circulation (ROSC) during chest compressions during sustained inflation (CC+SI) in asphyxiated newborn piglets.

Methods

Thirty term newborn piglets (1-3 days old, 1.7-2.4 kg) were anesthetized, intubated, instrumented, and exposed to 30-min normocapnic hypoxia followed by asphyxia. Piglets were randomized into three groups: CC+SI+18% (n = 8), CC+SI+21% (n = 8), or CC+SI+100% (n = 8), and a sham group (n = 6). Cardiac function, carotid blood flow, cerebral and renal oxygenation as well as respiratory parameters were continuously recorded throughout the experiment.

Results

When compared with the CC+SI+100% group, both CC+SI+18% and CC+SI+21% groups had similar times to ROSC and mortality. All three intervention groups had similar hemodynamic recovery by the end of 4 h observation period. Alveolar oxygen concentration was significantly lower in CC+SI+18% and CC+SI+21% compared to CC+SI+100% (p=0.004 and p=0.005, respectively).

Conclusion

Lower oxygen concentrations during chest compressions result in similar time to ROSC and mortality. Clinical trials are warranted to examine different oxygen concentration on newborn infants.

Funded By: Office of the Provost and VP Academic Summer Research Award

Abstract #: 68
Presenter: Deandra Luong
Supervisor: Georg Schmölzer
Title: Electrocardiography versus auscultation to assess heart rate during pulseless electrical activity in newborn infants
Authors: Deandra Luong, Po-Yin Cheung , Megan O'Reilly, Tze-Fun Lee, Georg Schmölzer
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Background: In 2015, the neonatal resuscitation guidelines incorporated the use of electrocardiography (ECG) to monitor heart rate (HR) of newborns. However, previous studies have indicated that cardiac arrest with pulseless electrical activity (PEA) rhythm may occur in the delivery room, rendering this method problematic.

Objectives: To evaluate the accuracy of ECG and auscultation in assessing HR during PEA.

Methods: A total of 45 piglets (age 0-3days, weight 1.7-2.4kg) were exposed to 30min normocapnic alveolar hypoxia followed by asphyxia until asystole, achieved by disconnecting the ventilator and clamping the endotracheal tube. During asphyxia, HR was assessed using auscultation, ECG, and carotid blood flow (CBF). At the time of asystole (defined as zero CBF), HR auscultated using a neonatal/infant stethoscope was compared to ECG traces.

Results: The median (IQR) duration of asphyxia was 402 (70-600) sec. In 8 (18%) piglets, CBF, ECG, and auscultation identified asystole. In 22 (49%) piglets, no CBF and no audible heart sounds were observed, whilst ECG displayed an HR ranging from 17-75/min. 15 (33%) piglets remained bradycardic (defined as HR of <100/min) after 10min of asphyxia, which was identified by CBF, ECG, and auscultation.

Funded By: Heart & Stroke Foundation; SickKids Foundation in partnership with the Canadian Institutes of Health Research

Abstract #: 69
Presenter: Olivia Kara Loewen
Supervisor: Paul Veugelers
Title: Adherence to recommendations for lifestyle behaviours in childhood and mental health in subsequent years: A prospective study of Canadian children
Authors: Olivia Kara Loewen , John Paul Ekwaru, Erin Faught, Katerina Maximova, Arto Ohinmaa, Paul Veugelers
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Mental health disorders affect over 15% of Canadian adolescents. To inform prevention strategies, we examined the associations of meeting established recommendations for diet, physical activity, sleep, and sedentary behaviour with mental health in adolescence.

Methods: Population-based prospective study (*N*=3436) linking 2011 health behaviour survey data among 10-11 years old adolescents with administrative health data from 2011-2014. Lifestyle behaviours were measured with the Harvard Food Frequency Questionnaire and self- and parental-proxy reports, expressed as meeting recommendations for vegetables and fruit, grain products, milk and alternatives, meat and alternatives, saturated fat, added sugar, sleep, screen time, and physical activity. Mental health was defined by physician diagnosed internalizing, externalizing, and other mental health disorders. Negative binomial regression was used to determine the independent and cumulative associations of meeting lifestyle recommendations with primary care contacts for mental health disorders.

Results: Of all participants, 12%, 67%, and 21% respectively met 1-3, 4-6, and 7-9 of the lifestyle recommendations, and 15% had a mental health diagnosis during follow up. Compared to participants who met 1-3 recommendations, those who met 7-9 recommendations had 56% lower Rate Ratio (RR) of primary care contacts for mental health during follow-up (RR:0.44 [95%CI: 0.31, 0.62]). For every additional recommendation met, the RR for primary care contacts for mental health decreased by 15% (RR:0.85 [95%CI:0.79, 0.91]).

Conclusions: Mental health disorders in adolescence may be reduced through compliance with lifestyle recommendations, with greater reductions as more recommendations are met. Emphasizing lifestyle recommendations may reduce the burden of mental health in primary care.

Funded By: WCHRI Trainee Travel Grant; CIHR, Alberta Innovates

Abstract #: 70
Presenter: Nate Nadolski
Supervisor: Jennifer Hocking
Title: Flux-dependent morphogenesis of zebrafish photoreceptors
Authors: Nate Nadolski, Sean McKenzie, Andrew Waskiewicz, Jennifer Hocking
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION

Photoreceptors are the light-detecting cells in the eye that enable us to visualize our surroundings. Highly sensitive rod photoreceptors are responsible for dim light vision, while cones provide high acuity colour vision. Their morphology consists of a sensory region, the outer segment, and a metabolically active inner segment. The outer segments contain stacks of disks laden with proteins of the phototransduction cascade.

Our lab has recent data linking downregulation of *kcnv2b*, a zebrafish gene that encodes a potassium channel subunit, with altered photoreceptor morphology: shortened cone outer segments and expanded rod outer segments. Interestingly, mutations in the human homologue KCNV2 cause a rare disease known as Cone Dystrophy with Supernormal Rod Response (CDSRR), characterised by early-childhood onset, photophobia, and night blindness, but also by a unique elevated rod response to bright light when recorded by electroretinogram.

We hypothesize that the patient phenotype is caused by changes in photoreceptor morphology. This project has two goals: explore the underlying disease mechanism in CDSRR while investigating the novel idea that current flow modulates outer segment growth.

METHODS

To relate these mutants to CDSRR, electroretinogram (ERG) will be used to characterize mutant photoreceptor electrical responses. Additionally, we are currently developing CRISPR mutants for *kcnv2a*, a paralog to *kcnv2b*. This opens the door for examination of *kcnv2a* individually and as part of a double knockout fish. The mutants will be crossed to transgenic lines with photoreceptor-specific fluorescent proteins, facilitating the analysis of morphology. To further characterize these genes, we plan to overexpress *kcnv2a* and *kcnv2b* specifically in rods or cones and test how modulation of the current in the opposite direction affects outer segment morphology. Finally, we will examine the expression of *kcnv2a* and *kcnv2b* in the zebrafish retina by *in situ* hybridization on adult tissue sections. This will indicate where the gene product is being transcribed and hints at the final protein's location.

EXPECTED RESULTS

We expect that *kcnv2* knockouts will exhibit similar ERG outputs as patients with CDSRR. Building off of our previous data, we anticipate dismorphic photoreceptor outer segments in *kcnv2* mutants. Lastly, we expect the overexpression of *kcnv2* will result in an equal and opposite phenotype to the knockouts.

CONCLUSIONS

Photoreceptors are elaborately constructed cells that can only be studied in living systems. The development of *kcnv2* mutant fish will allow us to study the disease mechanism of CDSRR while concurrently elucidating how these cells are built and maintained.

Funded By: Alberta Innovates Health Research

Abstract #: 71
Presenter: Neelam Punjani
Supervisor: Elizabeth Papathanassoglou
Title: A protocol to explore mental health issues related to sexual health among adolescent girls
Authors: Elizabeth Papathanassoglou, Kathleen Hegadoren, Zubia Mumtaz, Margot Jackson , Saima Hirani
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Background

Sexual health incorporates a wide range of interlinked mental, physical, and emotional factors. Sexual health and sexuality issues can affect a woman's physiological and psychological well-being, as well as her family, relationships, occupational functioning and her own hopes and fears. The bi-directional links between sexuality and mental health have only been recently recognized; as such research in this important aspect of adolescent girls' and their families' well-being is almost non-existent. Mental health concerns such as depression and anxiety are prevalent in adolescent population group however the role of sexuality in those has not been explored. These mental health issues may precipitate risky sexual behaviour, with the impeding risks of unwanted pregnancies, sexually transmitted infections, substance abuse and violence

Research Purpose

The study aims to explore the relationship of sexuality-related issues to depression and anxiety symptoms sexual health-related stress and anxiety among adolescent girls in Pakistan. Specific aims include to: a) investigate issues related to sexual health that may be perceived as stressors by adolescent girls, b) increase understanding of the lived experience of adolescent girls in their developing sexuality and the consequences of sexuality-related stressors and responses, c) explore participants' perceptions on what approaches would help them to successfully adjust and cope with those stressors.

Methodology

The Interpretive Description (ID) approach will be used to study the complex phenomena of mental health and sexual health in depth, in order to go beyond the evidence and search for what else might be there through the lens of Pakistani adolescents. A purposive sampling strategy will be used to enrol adolescent girls (age: 15-19 years) from high school in Karachi, Pakistan. Adolescent girls will be interviewed using a semi-structured interview guide to collect data regarding their perceptions of mental health issues as related to adolescent sexuality. Sample size will depend on data saturation. In parallel, the Perceived Stress Scale (PSS) data will be collected from the same participants to score the intensity of sexuality-related mental health stress among adolescent girls. An iterative and inductive analysis approach will be used as encouraged by ID design.

Expected Outcomes

The results of this research hold the potential to contribute to an integrated approach to adolescents' mental and sexual health and the development of future policies, strategies, services and training. They will also provide valuable preliminary evidence on the perceptions of sexuality-related stress and the consequences of such stress among adolescent girls. Moreover, I intend to develop a multilevel knowledge translation plan to ensure that key messages are developed for specific audiences.

Funded By: Aga Khan Foundation

Abstract #: 72
Presenter: Sarah Raza
Supervisor: Lonnie Zwaigenbaum
Title: Behavioural and physiological measures of emotion in infants at risk for Autism Spectrum Disorder
Authors: Sarah Raza, Lori-Ann Sacrey, Vickie Armstrong, Lonnie Zwaigenbaum, Susan Bryson, Jessica Brian, Isabel Smith, Azadeh Kushki
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION

Autism Spectrum Disorder (ASD) is associated with impaired emotional regulation, defined as the ability to maintain homeostasis in response to positive and negative events (Cole et al., 1994). Prospective studies of high-risk (HR) infants (i.e., have an older sibling with ASD) who later receive a diagnosis have shown differences in the ability to regulate their emotional states by 12 months of age (Garon et al., 2009; Bryson et al., 2017). The early control of emotion may be critical to the development of later social-communicative ability and consequently, the onset of ASD symptomology. The present study's objective was to determine whether infants' heart rate and observed affect are congruent during emotion-evoking tasks, and whether affect and/or heart rate predicts ASD symptom presentation in HR infants.

METHODS:

Participants: HR infants (n=35) who were assessed at 12 months of age. ***Experimental Measures:*** (1) *Emotion Regulation*:An observational assessment (adapted from LabTAB) comprised of activities designed to elicit positive (bubbles, toy play) or negative (toy removal, masks, grooming) emotions (Goldsmith et al., 1996). Infant affect was coded using Noldus Observer software, and heart rate was collected during each activity. Affect was coded for valence (positive, negative, or neutral) and intensity (to differentiate mild/moderate displays from extremely intense displays of affect). (2) *ASD Symptom Expression*: The Autism Observation Scale for Infants (AOSI; Bryson et al., 2007) is a clinician-led observational assessment of early signs of ASD. ***Analytical Approach:*** Average values were calculated for affect and heart rate. Data were analyzed using correlations to determine the relationship between affect and heart rate, as well as between affect intensity and heart rate with AOSI total score.

RESULTS

A significant correlation between heart rate and affect was found for toy play (r=.34, p=.05) and grooming (r=-.49, p=.003), but not other activities (ps>.05). Affect was significantly correlated with AOSI score for bubbles (r =-0.71, p<0.001), masks (r=-0.45, p<0.007), toy play (r=-.35, p=.04), and grooming (r=-0.57, p<0.001). No significant relationship was seen between heart rate and AOSI scores.

CONCLUSION

These preliminary results suggest small-to-modest congruence between internal (heart rate) and external (affect) signs of emotion regulation, where facial affect, rather than heart rate, predicted ASD symptom expression in 12-month-old HR infants. In the future, we may be able to discern behavioral and physiological differences between infants who are diagnosed with ASD from those who are not using this novel approach.

Funded By: WCHRI Graduate Studentship; Start-up/Retention Funding; CIHR; Alberta Innovates Brain Canada, Azrieli Foundation

Abstract #: 73
Presenter: Chelsea Durber
Supervisor: Christina Rinaldi
Title: Comparing maternal emotion socialization, meta-emotion, and children's emotional functioning in divorced and non-divorced families
Authors: Chelsea Durber, Christina Rinaldi
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Mothers nurture children's healthy emotional development through a process called emotion socialization (ES)[1]. Mothers' underlying beliefs about their own and their children's emotions, known as meta-emotion (ME), guide maternal ES[2]. Supportive maternal ES and ME promote children's healthy emotional functioning[3]. Approximately 1.2 million divorced or separated Canadians have children 18 years or younger[4], with female-parent families comprising 73% of the single-parent families with children[5]. Parenting quality is a key predictor of children's functioning in divorced families[6]. Post-divorce may present as a time where children especially need to draw on their resilience and emotional skills to navigate life; however, little is known about maternal ES and ME in divorced, female, single-parent families. I aim to answer the following research questions: 1) how do divorced and non-divorced mothers' ES and ME effect and predict children's resilience; and 2) are there differences between divorced and non-divorced mothers' ES and ME?

Method: I will use a quasi-experimental research design. Power estimates suggest a total sample of 210 mothers who self-identify as divorced (n=105)[7]. Mothers must have a child between the ages of 9 to 12 years, which is an important period in children's emotional development[8]. Participants will be recruited through child-related organizations and divorce-related community spaces. Maternal ME, ES, parenting and life stress, and social support will be assessed using the following maternal, self-report measures, respectively: PBACE[9], CCCNES[10], PSI[11], PSS[12], and the MPSS[13]. Children's resilience, emotion regulation, and socio-emotional functioning will be measured using the following self, parent, and teacher-report measures, respectively: RSA[14], ERC[15], and the SDQ[16]. Children will also complete the PRQ[17], which assesses their perceptions of the parent-child relationship. Two-way ANCOVAs will assess the interaction and main effects of maternal ES and ME on children's resilience, controlling for children's emotion regulation and social-emotional functioning. Based on previous research on children's externalizing behaviours, we will also conduct regression analyses that will test whether divorced and non-divorced mothers' ES and ME predict children's resilience, emotion regulation, and perceptions of the parent-child relationship. Finally, paired samples t-tests will determine whether divorced and non-divorced mothers differ in their ES and ME.

Results: This study is currently in the design phase. While there are no findings to share at the present time, feedback on the study design is welcome.

Conclusions: These findings will support a large community of mothers and children by elucidatingthe factors that promote positive parenting behaviours and children's resilience following divorce.

Funded By: WCHRI Graduate Studentship; Social Sciences and Humanities Research Council

Abstract #: 74
Presenter: Christina Y. Le
Supervisor: Jackie L. Whittaker
Title: Measuring health-related quality of life in active youth: a systematic review of available instruments
Authors: Linda K. Truong, Christopher J. Holt
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Health-related quality of life (HRQOL) is a complex and dynamic concept that encompasses an individual's perception of his or her overall well-being. The assessment of HRQOL is important to determine the efficacy of healthcare interventions and monitor changes in health status. There is evidence to suggest youth who experience a sport-related injury report poorer HRQOL compared to their uninjured peers. Before developing strategies to mitigate this decline in HRQOL, we must be certain that we are using psychometrically sound and relevant instruments to measure HRQOL in this unique population. Therefore, the objective of this systematic review to identify the most suitable instrument for assessing HRQOL in active youth by identifying available HRQOL instruments, evaluating their measurement properties, and determining their clinical application.

Methods: This systematic review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered in the PROSPERO database. Medline, CINAHL, Scopus, SPORTDiscus, and PEDro will be searched using a strategy developed in consultation with a librarian scientist. Records will be included if they contain original data, utilize a patient-reported HRQOL instrument, examine youth (10-24 years) who are active in sport and recreational activities, and are written in English. Two independent raters will complete record screening, data extraction, and instrument quality assessment. For all identified tools, the methodology of the measurement properties will be assessed using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist and the results of the measurement properties will be assessed using Terwee's quality criteria and Park et al. (2013) structural validity criteria.

Results: 1720 records were identified in the pilot search. Approximately 90 records are expected to meet inclusion criteria. Data collected from relevant studies will include: sample characteristics (e.g., age, sex, injury diagnosis), HRQOL instrument (i.e., type of instrument, intended use, type of respondent, number of dimensions and items), and measurement properties of instrument (e.g., reliability, validity, responsiveness, and interpretability).

Conclusion: The identification of the instrument(s) best suited to assess HRQOL in active youth who are at an increased risk of sustaining a sport-related injury is required to monitor changes in HRQOL following injury. Establishing accurate assessment of HRQOL is a necessary step that will inform the development and evaluation of interventions aimed at improving long-term well-being.

Funded By:

Abstract #: 75
Presenter: Jens Herzog
Supervisor: Andrew Waskiewicz
Title: The role of Tsc2 on eye development
Authors: Jens Herzog, Kevin Yoon, Xaverie Maclennan, Andrew Waskiewicz
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction:

Superior coloboma is a congenital blinding disorder, which is caused by aberrant embryonic morphogenesis of a fissure in the superior eye. From whole genome sequencing of patients presenting superior coloboma, our lab has identified a genetic variant of Tuberous Sclerosis Complex 2 (*TSC2*), a known regulator of mTOR signaling. We will test the hypothesis that tsc2 functions as a critical regulator of superior fissure morphogenesis.

Methods/Approach:

Eye development amongst vertebrates is highly conserved. This permits the use of zebrafish (*Danio rerio*), as a genetic model organism to study human eye development. As an initial study of Tsc2 function, we utilized gene-specific morpholino oligonucleotides to block Tsc2 translation. In addition, I plan to create a *tsc2*$^{-/-}$ fish using CRISPR-Cas9 mutagenesis to delete Tsc2 exon 1. This would provide an excellent model for further experiments assessing the effect on mTOR activity and to identify the mTOR outputs that are perturbed.

Results/Findings:

In addition to the whole genome sequencing, other individuals who have tuberous sclerosis complex (caused by Tsc2 mutations), have been reported to have atypical coloboma. We have demonstrated that Tsc2 knock-down by morpholino in zebrafish, causes a 60% incidence of superior fissure closure delay. The specific functional role of mTOR in the superior eye, though remain largely unknown, beyond the multiple general roles it plays in cell proliferation and growth as the outputs in the superior eye have yet to be assessed.

Conclusions:

The preliminary data indicates that Tsc2 knockdown increases the incidence of superior coloboma in zebrafish, suggesting that the human *Tsc2* mutations cause the developmental defect. With current genetics techniques we have the capability of creating a useful model of superior coloboma in zebrafish, and the role of mTOR signalling on eye development.

Funded By: WCHRI Innovation Grant; CIHR

Abstract #: 76
Presenter: Syed Benazir Alam
Supervisor: Qiumin Tan
Title: Investigation into the role of transcription factor capicua in autism spectrum disorder.
Authors: Syed Benazir Alam, Spencer Balay, Qiumin Tan
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Background: Autism spectrum disorder (ASD) is a developmental disease that affects social behaviour and communication. ASD is often associated with dysfunctional Ras/MAPK (rat sarcoma/mitogen-activated protein kinase) pathway. The Ras/MAPK pathway regulates gene expression in response to neuronal activity, but how it contributes to ASD pathogenesis is unknown. Ras/MAPK signaling can be switched on or off by the transcription factor capicua. Capicua is a high confidence autism risk gene and importantly, it regulates social behavior in mice and humans. Mice lacking capicua in the hypothalamus, a brain region that controls important aspects of social behavior, have prominent social interaction deficits. Moreover, ASD has been reported in people missing one functional copy of capicua. However, the molecular mechanisms by which capicua contributes to ASD pathogenesis remains unclear.

Rationale: Given the importance of Ras/MAPK pathway in neural activity-dependent transcription, I will examine the function of capicua in activity-dependent gene regulation.

Hypothesis: Capicua regulates neural activity-dependent transcription and social hormone synthesis.

Methods

Capicua was deleted from hypothalamus using brain-specific gene targeting strategy. RNA-seq studies were conducted in control and hypothalamic capicua-knockout mice brain to look at the levels of selected activity-dependent transcription genes such as negative feedback regulators of the Ras/MAPK pathway. *In situ* mRNA hybridization experiments were conducted, to look at the levels of "first responders", *c-Fos* and *Egr1* that control activity-dependent gene expression networks. Quantitative RT-PCR experiments were conducted was conducted to look at the levels of social hormones oxytocin and arginine vasopressinin control and hypothalamic capicua-knockout mice brain.

Results

Preliminary work from our lab shows that hypothalamic capicua-knockout mice exhibits impaired neural activity-dependent transcription as well as reduced levels of negative feedback regulators of the Ras/MAPK pathway and social hormones, oxytocin and arginine vasopressin.

Conclusion

Discussion: Based on our preliminary results, we suggest that capicua modulates social interaction in ASD patients by modulating negative feedback regulators of the Ras/MAPK pathway as well as social hormone network.

Summary: Ourexperiments will help gain mechanistic insight into the etiology of ASD due to dysfunctional Ras/MAPK or lower levels of social hormones, and facilitate future targeted therapeutic interventions.

Future direction: To uncover global activity-dependent transcription network, transcriptomic studies on un-stimulated and stimulated neurons will be conducted on hypothalamic capicua-knockout and control mice. Also by non-invasively manipulating neuronal activity, future experiments will test if stimulation of neurons with sluggish activity increases the level of social hormones and ultimately rescues social interaction deficits.

Funded By: Faculty of Medicine and Dentistry, Department of Cell Biology, University of Alberta

Abstract #: 77
Presenter: Timothy Fu
Supervisor: Joseph Casey
Title: SLC4A11 as a potential reactive oxygen species transporter
Authors: Timothy Fu, Darpan Malhotra, Joseph Casey
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives

Corneal endothelial dystrophies are a major cause of blindness worldwide. Fuchs endothelial corneal disease (FECD) is the most common corneal dystrophy, occurring at a 4% lifetime incidence, and disproportionally affects women. Congenital hereditary endothelial disease (CHED) is a childhood onset disease, with symptoms appearing at or soon after birth. Mutations in the SLC4A11 gene can cause both FECD and CHED; SLC4A11 encodes a basolateral membrane protein in corneal endothelial cells (CECs). One function of SLC4A11 is to mediate water flux. This prevents edema in the corneal stroma and the blurring of vision that occurs with corneal endothelial dystrophies. SLC4A11 downregulation has been shown to increase intracellular reactive oxygen species (ROS) levels and decrease cell viability in CECs. Because peroxides are similar to water in chemical structure and size, we hypothesized that SLC4A11 also plays a role in transporting ROS in CECs. Our goal is to identify if SLC4A11 transports ROS, which would be a critical role in maintaining CEC health.

Methods

Fluorescent, cytosolic oxidation-state sensor, roGFP2-Orp1, was used to measure intracellular ROS levels in live cells. HEK293 cells were co-transfected with cDNA encoding roGFP2-Orp1 and either SLC4A11, or Aquaporin 3 (AQP3), a known peroxide transporter, or empty vector. Expression of roGFP2-Orp1 and SLC4A11 was maximized by co-transfection under a range of conditions, followed by immunoblotting. roGFP2-Orp1 fluorescence in HEK293 cells was tracked in real-time with a fluorimeter, under two different conditions: (1) during active peroxide buffer perfusion, where rate of peroxide influx was measured, and (2) following treatment with ROS-generating drug, paraquat, where oxidation state following intracellular generation of ROS was measured.

Results

From the immunoblot, the optimum cDNA amounts for co-expression were determined to be 0.9 µg SLC4A11/2.0 µg roGFP2-Orp1 cDNA and 1.8 µg AQP3/2.0 µg roGFP2-Orp1 cDNA. Using AQP3 as a positive control, we determined that SLC4A11 did not significantly increase the influx of peroxide. However, SLC4A11 transfected cells were at a significantly lower oxidation state following paraquat treatment compared to untransfected cells.

Conclusions

Our preliminary results showed that SLC4A11 did not increase peroxide influx rates, but decreased oxidation following intracellular ROS generation. This suggests that SLC4A11 may efflux excessive intracellular ROS. This could be a potential mechanism by which SLC4A11 maintains CEC health.

Funded By: WCHRI Summer Studentship

Abstract #: 78
Presenter: Matthea Sanderson
Supervisor: Rachel Wevrick
Title: Elucidating the function of MAGEL2 through its protein-protein interaction network defined by proximity labeling (BioID) and mass spectrometry
Authors: Matthea Sanderson, Richard Fahlman, Rachel Wevrick
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Mutations in the *MAGEL2* gene cause the neurodevelopmental disorder Schaaf-Yang syndrome. *MAGEL2* is also one of six genes inactivated in Prader-Willi syndrome, which shares many clinical features with Schaaf-Yang syndrome. In mice, loss of *Magel2* affects brain development and function, disrupts circadian cycles and causes other phenotypes that recapitulate endophenotypes in Schaaf-Yang and Prader-Willi syndromes. Mice lacking *Magel2* have region-specific reduction in brain volume and altered brain chemistry. However, little is known about the role MAGEL2 plays in physiology during development or in cell biology. We used proximity-dependant labeling (BioID) combined with mass spectrometry to elucidate the molecular and cellular pathways in which MAGEL2 participates.

Methods

We identified proteins that interact with MAGEL2 using BioID and mass spectrometry. Flp-In 293 cells were stably transfected with plasmid constructs expressing a biotin ligase (BirA*) MAGEL2 fusion protein. Proximity-labeled biotinylated proteins were recovered by streptavidin affinity purification and identified by mass spectrometry. Two MAGEL2 constructs were analyzed: FL-MAGEL2 encodes the 1249 amino acid full length human MAGEL2 protein, while Cterm-MAGEL2 encodes the C-terminal portion of the protein containing the MAGE homology domain. The C-terminal region has been previously studied, whereas this is the first study to examine protein interactions with the N-terminal region of the MAGEL2 protein.

Results

We identified sets of MAGEL2-interacting proteins that included both known interactors (e.g. USP7) and novel interactors. We compared the interactome of the FL-MAGEL2 protein with that of Cterm-MAGEL2. This revealed a set of proteins in the FL-MAGEL2 interactome that were absent in the Cterm-MAGEL2 interactome, suggesting that they interact with the N-terminal region of MAGEL2. We identified two families of proteins that interacted with FL-MAGEL2 (TNRC6 and YTHDF) that function in RNA silencing and mRNA stability respectively.

Conclusion

These results suggest a novel function for MAGEL2 in RNA biology through specific interactions with the N-terminal region of the MAGEL2 protein.

Funded By: WCHRI Graduate Studentship; CIHR, Foundation for Prader-Willi Research

Abstract #: 79
Presenter: Bingcheng Jiang
Supervisor: Michael Weinfeld
Title: Study of novel mutations in the DNA repair gene polynucleotide kinase/phosphatase (PNKP) and their role in cancer induction and neurological disorders
Authors: Bingcheng Jiang, Chibawanye I. Ene, Bonnie Cole, Jeff Ojemann, Sarah Leary, Mesfin Fanta, Sudip Subedi, Michael Weinfeld
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: The enzyme polynucleotide kinase/phosphatase (PNKP) plays a key role in DNA repair by resolving the chemistry at DNA strand breaks. Mutations in PNKP (chromosome 19q13.4) are known to cause MCSZ, a serious neurodevelopmental disorder, but to date there has been no link to cancer initiation or progression. However, a child with MCSZ recently presented at Seattle Children's Hospital with a 3-cm glioblastoma. The child was shown to have two germline mutations in PNKP.

Methods: To study the effects of the PNKP mutations found in this patient, we generated mutant PNKP cDNAs carrying either the individual mutations or the double mutation using site directed mutagenesis. These cDNAs were incorporated into bacterial and mammalian expression vectors. The bacterially expressed mutant proteins as well as the wild type have been purified and are undergoing testing for PNKP DNA kinase and phosphatase activity. The PNKP cDNAs, fused to GFP, were expressed in Hela PNKP knockout cell lines. High-content analysis and micro- irradiation techniques are being used to determine PNKP localization within the cells and recruitment to damaged DNA.

Results: Our preliminary results showed that the mutations altered the kinase and phosphatase activities of PNKP, especially the double mutant PNKP. In the GFP-PNKP transfected cells, the localization of mutant PNKP is also different from the wild type.

Conclusion: Neurological disease is one common consequence of DNA repair protein mutation or abnormal DNA repair response. Before this Seattle case, there was no study linking PNKP mutation to any kind of cancer. Due to the rarity of MCSZ, we might have underestimated the role of PNKP in carcinogenesis. Our results showed this novel PNKP mutation greatly changed the protein activities and localization, which could contributes to possible deleterious consequences, such as the neurological symptoms and carcinogenesis found in the patient.

Funded By: Canadian Institutes of Health Research

Abstract #: 80
Presenter: Vivien Obiakor
Supervisor: Anita Kozyrskyj
Title: Dose-dependent impact of infant antibiotic exposure on the gut microbiota composition at 12 months of age
Authors: Vivien C. Obiakor, Meghan B. Azad, T. Konya, David S. Guttman, Allan B. Becker, Piushkumar J. Mandhane, Theo J. Moraes, Malcom R. Sears, Stuart E. Turvey, Padmaja Subbarao, James A. Scott, Anita L. Kozyrskyj and the CHILD Study Investigators
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Greater prescribing of antibiotics to infants has coincided with an epidemic of allergic diseases in developed countries. Infant antibiotic exposure, as well as gut microbiota composition, are linked to future risk of asthma and obesity. Stronger association observed with multiple courses of antibiotics add to biological plausibility. The relationship between early life antibiotics and later childhood diseases may be explained by a disturbed gut microbiota. The purpose of this study was to determine the dose-response association between antibiotic exposure and gut microbiota composition in 12-month-old infants.

Methods

This study included a representative sample of full-term infants (n=190) in Manitoba from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. Infant antibiotic exposure was obtained from hospital records (maternal intrapartum, newborn) and the provincial prescription database (infant). Birth method was obtained from hospital records. Fecal samples were collected at 12 months and gut microbiota were profiled using illumina 16S rRNA sequencing. Spearman's correlation was used to measure the strength and direction of association between number of antibiotic courses and median abundance of gut microbiota.

Results

About 61% of infants had been exposed to antibiotics during their first year of life and over 12% had received 3 or more courses. Maternal intrapartum and intravenous administration to the newborn accounted for 47% of antibiotic exposure in infants. As the number of antibiotic courses increased, the median abundance of genus *Streptococcus*, *Dorea and Lachnobacterium* was observed to rise successively in gut microbiota. After stratification by birth method, more statistically-significant dose-related associations were observed in vaginally-born infants, seen as increased levels of *Lachnobacterium* (Spearman's correlation(r) = 0.20; p = 0.02) and decreased abundance of *Clostridia* (r = -0.22; p = 0.01), *Bacteroides* and *Ruminococcus*. In caesarean-delivered infants, *Blautia* and *Ruminococcus* were observed to decrease in abundance with antibiotic dose. Dose-related increases to the median abundance of *Enterobacteriaceae* were observed in both groups.

Conclusions

Multiple courses of antibiotics affect gut microbiota composition and this association is more pronounced in vaginally-born infants. Dose-dependent associations have been reported between antibiotics and childhood allergic diseases. Hence, affected gut microbes may play an important role in infant immunity and health outcomes.

Funded By: Canadian Institutes of Health Research

Abstract #: 81
Presenter: Carla Sosa Alvarado
Supervisor: Catherine Chan
Title: Antibiotic administration at early stages of life affects pancreatic beta-cell development and bile acids metabolism
Authors: Carla Sosa Alvarado, Kaiyuan Yang, Janelle Fouhse, Steven Qiu, Catherine Chan , Ben Willing
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives (50w)

Early life antibiotic exposure has been associated with adverse metabolic outcomes. We have previously demonstrated alterations in islet development and function in a piglet model of antibiotic exposure that resulted in reduced beta-cell area and insulin content long after antibiotic withdrawal. The objective of this study was to identify the mechanism through which antibiotics affect islet development.

Methods/Approaches (150w)

A piglet model was chosen due to similarities in gastrointestinal function and structure, and pancreas development in infants. Crossbred piglets (Duroc x Large white/landrace) were randomly selected to be treated with amoxicillin (30mg/kg/day) or placebo from birth to termination and sample collection at post-natal day 7. TGR5 is a bile acid receptor that when is activated by bile acids, induces GLP-1 secretion.

Gene expression of bile acids transporters, bile acid receptor TGR5, GLP-1 receptor, and pro-glucagon was measured from isolated islets, ileum, and distal colon. Plasma GLP-1 concentration was assayed by ELISA. To identify the effect of antibiotics on Beta-cell development, KI67 and TUNEL assay was performed in fixed pancreatic samples. Due to their role in the regulation of GLP-1 and pancreatic function, and the established impact of bacteria on the bile acid pool, gallbladder bile acids composition was measured by liquid chromatography-mass spectrometry.

Results/Findings (150).

Animals treated with amoxicillin presented higher GLP-1 concentration in plasma and GLP-1 receptor gene expression in islets. GLP-1 concentrations were not explained by differences in blood glucose. Moreover, hyocholic acid and its conjugated form were 2-fold higher in amoxicillin piglets vs control, providing one plausible mechanism through which plasma GLP-1 levels were elevated. TGR5 gene expression in islets from amoxicillin treated group was not different from the control group, however, gene expression of this receptor was reduced in the ileum (p.value 0.049).

Conclusions (50)

Administration of amoxicillin in piglets at early stages of life had an influence on GLP-1 secretion that may be mediated through changes in bile acid metabolism. Elucidating the molecular mechanism through which antibiotics affect beta-cell function and development will support novel strategies to reduce the long-term metabolic risks associated with early life antibiotic exposure.

Funded By: WCHRI Graduate Studentship; CIHR; Alberta Agriculture and Forestry

Abstract #: 82
Presenter: Robert Penner
Supervisor: Simon Urschel
Title: Monitoring immune suppression after pediatric transplantation with flow cytometric activation assays
Authors: Robert Penner, Lavinia Ionescu, Simon Urschel
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION: Post-transplant (Tx) management requires the use of an immunosuppressive combination therapy. Currently, drugs are adjusted to achieve target plasma trough levels or dosed by weight with no monitoring. Interestingly, patients with similar levels and doses of drugs may experience a variable extent of clinical immune suppression. The objective is to develop an *in vitro* method of quantifying immune suppression by evaluating lymphocyte activation after stimulation.

METHODS: Peripheral blood mononuclear cells (PBMCs) were isolated from 263 samples obtained from131 children listed for solid organ Tx as part of a national multi-center study (CNTRP POSITIVE). PBMCs were stimulated with Staphylococcal enterotoxin B (SEB) and viral antigens over 16 hours. Activation of CD4+ cells, reflected in enhanced CD69 expression and cytokine (IFNγ, TNFα, IL2) production, was assessed by flow cytometry. CD69 and cytokine expression levels were calculated as percent change from the unstimulated condition and compared with the level of immunosuppressive drugs.

RESULTS: Cytokine production levels in SEB-stimulated cells were highly correlated ($r=0.658$ to 0.874, $p<0.005$). Immune activation was significantly lower in patients with Tacrolimus levels >10 µg/L compared to those <10 µg/L ($p<0.05$). Immune activation was significantly lower at the 3-month ($p<0.01$) and 12-month ($p<0.001$) time points compared to pre-Tx.

CONCLUSION: The strong intra-sample correlations between cytokine levels indicate the assay is accurately identifying activated CD4+ cells. Decreased cytokine production post-Tx and with higher levels of immune suppression highlights the assay's ability to quantify the degree of immune suppression. This assay appears promising as a tool for adjusting immune suppression, however, it needs further longitudinal assessment and correlation to clinical outcomes.

Funded By: WCHRI Start-up or Retention Funding; Summer Studentship; CIHR; Alberta Transplant Institute

Abstract #: 83
Presenter: Tiffany Kim
Supervisor: Simon Urschel
Title: Lymphocyte subtype proportions and allergic disorders in children awaiting solid organ transplantation
Authors: Tiffany Kim, Lavinia Ionescu, Yaron Avitzur, Simon Urschel
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Children after transplantation (Tx) show an increased frequency of allergic disorders (AD) compared to healthy children. They depend on lifelong immunosuppression, and some undergo lymphocyte depletion at Tx, likely promoting AD. We previously found altered B and T cell patterns in children after heart Tx. We assessed whether these patterns are present pre-Tx by comparing the immune profiles of children awaiting various organ Tx with and without AD.

Methods: This study was part of the POSITIVE study, within the Canadian National Transplant Research Program. Clinical data were collected into a REDCap database. Peripheral blood mononuclear cells (PBMC) were isolated from patient blood via density gradient centrifugation and subtyped by flow cytometry with a focus on regulatory cells. Cell distributions were compared between patients with and without AD across kidney, heart and liver Tx groups (KTx, HTx, LTx) and in correlation to age.

Results: In 115 patients, 38% of KTx, 34% of HTx and 18% of LTx recipients experienced one or more allergic disorders (asthma, eczema, rhinitis) pre-Tx. AD patients had significantly higher proportions of naïve CD4+ memory T cells ($p < 0.001$) and significantly lower proportions of CD4+ memory effector T cells ($p = 0.007$) than patients without AD. They also had significantly higher proportions of CD27+IgM+ B cells ($p < 0.001$) and in trend higher proportions of CD45RA+CD27+ naïve regulatory T cells. Both groups showed increasing CD4+ memory and memory effector T cells with increasing age.

Conclusions: Prevalence of AD in children awaiting KTx and HTx is higher than in those awaiting LTx and over twice as high as in the general population. Already before Tx, higher prevalence of AD is associated with altered proportions of memory and regulatory cells and may be enhanced by immunosuppression post-Tx. Modified therapeutic regimes may benefit these patients.

Funded By: Alberta Transplant Institute (ATI)

Abstract #: 84
Presenter: Khushmol Dhaliwal
Supervisor: Lonnie Zwaigenbaum
Title: Assessing the role of appetite hormones in children with overweight and obesity and Autism Spectrum Disorder (ASD)
Authors: Khushmol Dhaliwal, Lucila Triador, Caroline Richard, Andrea Haqq, Lonnie Zwaigenbaum
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction:

Obesity and its associated complications are among the most common and severe health risks in children with ASD. Current literature on the rates of obesity and overweight in ASD reports a higher prevalence of obesity in children with ASD in comparison to children without ASD. Research suggests differences in specific satiety hormones in populations with ASD, in comparison to controls, such as a decrease in ghrelin and an increase in leptin concentrations. Although current research in this area is limited, it suggests the possibility of neuroendocrine influences on eating behaviors in children with ASD.

The aim of this study will be to assess for differences in hormones (ghrelin, leptin, GLP-1, insulin) and glucose in ASD, that may contribute to the development of overweight/obesity in this population, in comparison to typically developing, control populations.

Methods:

Participants aged 5-12 years old will complete one study visit to the Clinical Research Unit at the University of Alberta. Anthropometric measurements (height, weight, and waist circumference) will be completed during the visit. Participants will be assigned to one of the four groups: obese/overweight and ASD, normal weight and ASD, obese/overweight and without ASD, and normal weight and without ASD. Participants will fast for 8 hours prior to the study visit. During the visit, blood will be drawn and later assessed for hormone concentrations (ghrelin, leptin, GLP-1, insulin) and glucose. Participants will also complete a Food Related Problems Questionnaire (FRPQ) in order to better understand any differences in challenging eating behaviors between ASD and typically developing populations.

Expected Results:

It is hypothesized that we are likely to find shifts in hormonal factors in children with ASD, when compared to typically developing controls. The different BMI groupings will allow for a better understanding of the independent effect of being obese/overweight and ASD on shifts in hormonal factors.

Through this study we hope to understand how key appetite hormones are affected and may be leading to weight gain in ASD.

Conclusions:

This study may provide further insight into specific biological drivers of increased weight gain in children with ASD and help to better understand the role of potentially modifiable factors, such as diet, and how they relate to the development of obesity. This could lead to the identification of novel prevention and treatment strategies and help to further explain why children and adults with ASD are at a higher risk of chronic health problems (e.g., diabetes, coronary heart disease).

Funded By: WCHRI Support services; Autism Edmonton and the Autism Research Centre

Abstract #: 85
Presenter: Kelsea Drall
Supervisor: Anita Kozyrskyj
Title: The use of acid-suppressive medications during infancy is associated with an 'allergic' shift in gut microbiota composition
Authors: Kelsea M. Drall, Amanda A. Lau, Hein M. Tun, Hien Q. Hyunh, David S. Guttman, Malcolm R. Sears, Puishkumar J. Mandhane, Padmaja Subbarao, Stuart E. Turvey, Allan B. Becker, Diana L. Lefebvre, James A. Scott, Anita L. Kozyrskyj, The CHILD Study Investigators
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives

The use of acid-suppressive medications during infancy is consistently linked to the development of allergic disease. The mechanism of this association remains unknown, but disturbances to the gut microbiota may play a role as intestinal bacteria are pH sensitive. This study aims to explore the relationship between the use of proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) and the fecal microbiota of infants with gastroesophageal reflux (GER) symptoms.

Methods/Approach

Infant medication use was reported in a medication questionnaire completed at 3 months postpartum for participants in the Canadian Healthy Infant Longitudinal Development (CHILD) cohort (N=3455). A subset of 1028 infants from the Vancouver, Edmonton and Winnipeg sites had complete medication questionnaires and a useable 3-month fecal sample, and were thus included in this study. Fecal samples were profiled using 16S rRNA sequencing and quantified using qPCR. Mann-Whitney U-tests were used to compare the median relative abundances of taxa and the Chao1 richness and Shannon diversity indices of GER medication users and non-users. Colonization (present yes/no) with *Clostridium difficile* was evaluated using fisher's exact tests.

Results/Findings

5.15% of infants reported using an acid-suppressive medication (3.89% H2RA and 1.26% PPI). Compared to non-medicated infants, those receiving a PPI had an increased abundance of Lachnospiraceae (p=0.05), Streptococcaceae (p=0.01, also p=0.02 with H2RA) and reduced Bifidobacteraceae (p=0.07). Furthermore, 51.43% of infants receiving an H2RA were colonized *Clostridium difficile*, compared to 48.57% of non-users (p=0.016). Consequently, those who received a H2RA had 2.32 greater odds of being colonized with *C. difficile* compared to un-medicated infants (OR: 2.23, 95% CI: 1.18-4.56, p=0.015). Microbial richness and diversity were not different between groups. All findings remained largely unchanged following stratification and adjustment for feeding mode and infant use of antibiotics, suggesting robustness in these findings.

Conclusions

Decreased abundance of Bifidobacteraceae and colonization with *C. difficile* are characteristic of infants with an increased risk of allergy and asthma. Our study suggests that the use of acid-suppressants during infancy is not without consequence and the impact on the gut microbiota and future health need to be considered when prescribing these medications.

Funded By: CIHR

Abstract #: 86
Presenter: Shima Afhami
Supervisor: Andrea Haqq
Title: Gut microbiome composition and function in North-American children with and without Prader-Willi Syndrome
Authors: Shima Afhami, Lucila Triador, Edward Deehan, Karen Madsen, Jens Walter, Andrea Haqq
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Prader-Willi Syndrome (PWS) is the most common syndromic form of childhood obesity and is characterized by failure to thrive during infancy followed by abnormally increased appetite (hyperphagia) and progressive obesity. The pathogenesis of hyperphagia and weight gain in PWS is poorly understood and management strategies have been met with variable and limited success. Several studies support an etiological contribution of dysbiotic gut microbiota in the metabolic derangements of obesity; however, the specific role of the gut microbiome in PWS and childhood obesity is not fully understood. This study aims to identify and characterize the bacterial composition present in children with and without PWS as this is an important first step to guide the design of effective therapies targeting the gut microbiome to achieve weight control and management of hyperphagia. This is especially pertinent as there is currently no established effective therapy for PWS-related hyperphagia and obesity.

Methods: Children with PWS (ages 3-17 years, n=25) and age-, sex- and body mass index (BMI) percentile matched controls (n=25) were recruited. Stool samples, a 3-day dietary record, a hyperphagia questionnaire (validated in PWS), physical activity data, and anthropometric measures (height, weight and waist circumference) were collected. Co-variate information, including gestational age; birth history; infant feeding (breast versus formula-feeding); use of probiotics, and medications was also collected. Analysis of partial 16S rRNA sequence reads obtained by MiSeq sequencing (Illumina) will be obtained to allow characterization of fecal microbiota composition at phylum, family, genus and OTU (proxy for bacterial species) level. α and β-diversity indices as well as short chain fatty acid (SCFA) profiles will be determined and contrasted between groups.

Preliminary Results: We have enrolled 25/25 children with PWS (14F:11M; median age = 6.4 (3 to 17y); median BMI percentile = 78.5; 15 deletion: 10 uniparental disomy) and 25 healthy control children (9F:16M; median age = 8.8 (3 to 17y); median BMI percentile = 77.6). We expect to see functional and structural difference in the gut microbiota composition of children with and without PWS. In addition, we hope to gain further insight on the SCFA profiles of individuals with PWS, as a decreased relative abundance of SCFAs have been implemented in satiety and as a contributing factor to metabolic complications including Type 2 diabetes and obesity.

Conclusion: Gaining a better understanding of the gut microbial profile of children with PWS has the potential to unveil more personalized approaches for effective treatment of excessive weight gain and hyperphagia associated with PWS to improve overall health and quality of life.

Funded By: WCHRI Partnership resources; Support services; CIHR; Alberta Innovates; PWSA

Abstract #: 87
Presenter: Sydney St. James
Supervisor: Alicia Chan
Title: Case report: Improved creatine kinase with decreased simple and supplemental carbohydrate intake in two siblings with Glycogen Storage Disease IIIa.
Authors: Sydney St. James, Alicia Chan
Affiliations: Other
Research Activity: Children's Health and Well-Being

Objective: We describe two siblings with Glycogen Storage Disease IIIa (GSD IIIa) with a significant improvement of creatine kinase (CK) following a decrease in simple and supplemental carbohydrate intake.

Methods: Two male siblings (age 13 and 8 years) were diagnosed with GSD IIIa. The older sibling was diagnosed at 4 years and the younger sibling after birth. Both siblings developed increased CK levels greater than 2500mmol/L. The younger sibling also developed hypertrophic cardiomyopathy at 5 years and was started on cardiac medications. Over 29 months, treatment included decreasing simple and supplemental carbohydrate while maintaining euglycemia; a high protein diet was continued. Significant reduction in simple carbohydrate intake was confirmed by food record analysis. The older sibling completely eliminated supplemental cornstarch. The younger sibling eliminated daytime cornstarch however required 0.6g/kg of Glycosade to maintain euglycemia overnight.

Results: In both siblings, CK levels decreased significantly. The older sibling's CK decreased from 2955mmol/L to 334mmol/L. The younger sibling's CK decreased from 3507 mmol/L to 427mmol/L. The younger sibling's recent echocardiogram showed stabilization of his hypertrophic obstructive cardiomyopathy.

Conclusion: We present two siblings with GSD IIIa who benefited from a decrease in simple and supplemental carbohydrate intake. This was demonstrated by a decrease in CK levels and no adverse effects were observed. Of note, their previous high protein diet did not result in a decrease in CK. Further follow-up will determine if this intervention also had a positive effect on the younger sibling's cardiomyopathy and their risk for myopathy.

Abstract #: 88
Presenter: Maha Alsaif
Supervisor: Andrea Haqq
Title: The impact of a high-protein diet on diet-induced thermogenesis and substrate oxidation in Prader-Willi syndrome: preliminary findings
Authors: Maha Alsaif, Sarah Elliott, Mohammadreza Pakseresht, Michelle L Mackenzie, Carla M Prado, Catherine J. Field, Andrea M Haqq
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Meals of similar caloric content but differing in macronutrient composition may impact diet-induced thermogenesis (DIT), likely influencing total energy expenditure (TEE). Energy expended through digestion, absorption and storage of dietary protein is higher than for carbohydrate and fat. Therefore, a high-protein (HP) diet could have an influence on energy metabolism and weight control. Therefore, the aim of this study was to compare the impact of a HP diet versus a typical North American, high-carbohydrate diet on DIT and substrate oxidation in individuals with Prader-Willi syndrome (PWS).

Methods: Participants completed three separate study visits. Anthropometric measurements were completed at each study visit. In a randomized, crossover study design participants were allocated to two isocaloric arms: a) standard diet: 55% carbohydrate, 15% protein, and 30% fat; b) HP diet: 20% of carbohydrate, 50% protein, and 30% fat. Participants received the prescribed diets (three meals plus snacks per day accompanied by either a powder supplement (high protein diet test) or a snack (standard diet test) for one day prior to each study visit and a breakfast meal inside the whole-body calorimetry unit (WBCU). Diets were designed to ensure participants were in energy balance. Resting metabolic rate (RMR), DIT and respiratory exchange ratio (RER) were assessed. Differences between diets were assessed by paired sample T-test or Wilcoxon matched pairs test, as appropriate, considering a critical significance value of $p<0.05$.

Results: Four individuals with PWS (3F/1M, age: 14.5±4 (11-20 years)), BMI percentile: (82.4+10 (70.2-91) and body mass index: 40.3 kg/m^2) were assessed. No differences were observed in the DIT measurements between HP and standard diets (258±157 vs 231±119 kcal; p=0.66). However, the HP diet resulted in a lower RER in comparison to the standard diet (0.81±0.14 vs 0.86±0.19; $p<0.038$).

Conclusion: RER was lower in the HP dietcompared to the standard diet in individuals with PWS; suggesting a shift towards fat rather than carbohydrate as a fuel source. However, due to the small sample size meaningful statistical considerations are not possible at this time. This preliminary data suggests a diet higher in protein may provide a metabolic advantage compared to a typical North American, high-carbohydrate diet. Future analysis of healthy children matched for age, sex and BMI percentile will confirm if individuals with PWS metabolize food differently as compared to healthy children.

Funded By: WCHRI Innovation Grant

Abstract #: 89
Presenter: Janelle Fouhse
Supervisor: Benjamin Willing
Title: Early life antibiotics alters long-term innate immune response despite transient microbial changes
Authors: Janelle Fouhse, Kaiyuan Yang, Juan More Bayona, Susan Goruk, Arun Kommadath, Graham Plastow, Paul Stothard, Catherine Field, Daniel Barreda, Benjamin Willing
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Early life microbial composition plays a significant role in immune development and function with perturbations caused by early life antibiotic exposure being associated with immune mediated diseases later in life. Our objective was to elucidate the relationship between neonatal antibiotic exposure on microbiota and subsequent immune system development using a piglet model.

Methods

Newborn piglets were exposed to a therapeutic dose (30mg/kg) of amoxicillin (AB) from post-natal day (PND)0 to 14, mimicking typical childhood exposure. Successional microbial patterns, blood gene expression, *ex vivo* immune cell response, and immune response kinetics to an intraperitoneal (IP) *Salmonella enterica* serovar Typhimurium challenge on PND49 were evaluated.

Results

AB exposure caused a significant change in fecal microbial composition on PND3 due to a 105% increase in *Enterobacteriaceae* with live cecal coliform counts on PND7 indicating a 10-fold increase. The shift in microbial composition was transient and successional patterns normalized by PND14. *Ex vivo* stimulation of isolated peripheral blood mononuclear cells on PND 21,49, and 84 with a T-cell mitogen revealed increased interferon-gamma (IFNγ) secretion in AB exposed piglets. When intraperitoneally challenged with heat-killed *Salmonella*, immune cells infiltrating the peritoneal cavity isolated from AB piglets showed more rapid activation, indicated by increased NF-κB translocation. Expression of IFNγ at 4h, and interleukin (IL)-2 and IL-6 at 12h were greater post-challenge in peripheral blood of AB exposed piglets.

Conclusion

Overall, early life amoxicillin exposure resulted in a more responsive immune cell population, despite effects on the microbiota being transient. Since amoxicillin is a commonly prescribed childhood antibiotic, results indicate the necessity for caution in early life antibiotic treatments, and the need for further understanding mode of action to prevent adverse effects of this necessary and life-saving treatment.

Funded By: CIHR; Alberta Agriculture and Forestry, Genome Alberta, NSERC

Abstract #: 90
Presenter: Jeremy Jerasi
Supervisor: Michael Bording-Jorgenson
Title: Effects of dietary fiber on symptom severity in Inflammatory Bowel Diseases: a preliminary in-vitro analysis
Authors: Jeremy Jerasi, Michael Bording-Jorgenson, Heather Armstrong, Eytan Wine
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: The causes of inflammatory bowel diseases (IBD), including Crohn Disease (CD) and Ulcerative Colitis (UC) are poorly understood. They are characterized by chronic inflammation of the bowel. Incidence is increasing, with 25% of new cases occurring in children. The microbiome is critical to human health, and changes in both its diversity and composition have been linked to IBD pathogenesis. Dietary fiber may play a critical role in linking the microbiome to disease pathogenesis. Many beneficial dietary fibers are indigestible for humans, and instead are fermented by microbes in the large bowel. My project aimed to establish preliminary data supporting the hypothesis that unfermented fibers, or fermentation by-products, may be detrimental in IBD by binding fiber receptors on the surface of immune cells, driving inflammation.

Methods: We utilized growth curves to evaluate the effect of oligofructose, inulin, maltodextrin (positive growth control), and cellulose (negative growth control) fibers on growth of patient-isolated bacteria. Bacteria chosen were found by the Wine lab to be implicated in IBD pathogenesis, as well as bound by IgG in the mucosa. E12 human intestinal epithelial cell lines were utilized as infection models, and gentamicin protection assays were used to quantify bacterial invasion in response to the fibers. An immunohistochemical stain against a macrophage fiber receptor, potentially linked to pathogenesis, was applied to 18 pediatric patient biopsies.

Results: After analyzing the growth curves, maltodextrin proved to be the fiber stimulating the most bacterial growth. Interestingly, oligofructose demonstrated similar, but slightly lower growth rates than maltodextrin across various tested bacteria. *Rumminococcus sp.*, previously shown by our lab to be a potential pathobiont, grew best on cellulose. Analysis of the gentamicin protection assays showed that *Burkholderia cepacia* (another pathobiont), was found to infect epithelial cells more when incubated with all tested fibers. Immunohistochemistry of 18 pediatric patient biopsies demonstrated an increase of disease-related fiber receptors in IBD patient tissues.

Conclusions: Here we demonstrate that undigested fibers affect both the growth and infectivityof select microbes implicated in IBD pathogenesis. Examination of the mechanism by which fiber affects bacterial invasion in the gut is key to advancing treatment. Furthermore, overexpression of fiber receptors in pediatric IBD patient biopsies demonstrates a possible role for these fibers in inflammation. Understanding the role of dietary fiber on the host immune response will provide an opportunity to improve IBD symptoms by utilising tailored dietary intervention to improve disease outcome.

Funded By: Canadian Association of Gastroenterology

Abstract #: 91
Presenter: Avery Crocker
Supervisor: Dr. William Craig
Title: Granulation tissue associated with pediatric gastrostomy tubes
Authors: Avery Crocker, Dr. William Craig
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction:

Gastrostomy tubes are nutritional support devices, inserted through the abdominal wall into the stomach. The introduction of gastrostomy tubes into common practice eliminated the need for prolonged nasogastric nutritional support. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends gastrostomy tubes in pediatric patients for whom nutritional support is anticipated for a minimum of four weeks. Pediatric patients who meet this criterion are most often chronically ill, and gastrostomy tubes are commonly utilized in short bowel syndrome, neurological disease, prematurity, congenital heart disease, and oncologic disease.

A complication of an existing stoma is granulation tissue. Granulation tissue formation is generally attributed to improperly sized devices, resulting in subsequent leakage, excessive inflammation and healing response. The ensuing and bothersome discharge, pain and infection may lead to eventual surgical debridement.

Granulation tissue at the gastrostomy site is of particular interest to us. The incidence of leakage and granulation tissue development at the stoma is contended among the literature. This adverse effect is often inconsistently reported in outcome studies, potentially due to a lack of a definitive grading system for quantification. Furthermore, it is not always considered a complication and documented.

Approach:

To determine the prevalence of granulation tissue, we initiated a prospective cohort study in the Pediatric Home Nutrition Support Clinic at the Stollery Children's Hospital. Patients with a pre-existing G-Tube are approached for the study, and a CRF completed collecting information regarding the presence of granulation tissue, suspected infection, care of the stoma, prior treatments and possible cofounding factors.

The data collected will be analyzed and the incidence of granulation tissue associated with gastrostomy tubes at this clinic will be calculated. Demographic and descriptive variables will be described using appropriate parametric or non-parametric techniques. Dichotomous variables will be analyzed using the chi-squared test or the Fischer's Exact test if expected cell count is less than 5. Continuous variables will be analyzed with the 2 independent sample t-test. Additionally, a logistic regression will be used to determine the related risk factors for the development of this granulation tissue, including patient behaviours, stoma condition, demographics and treatments attempted past and present. Testing for interaction and confounding will be completed. A P-value less than 0.05 will be considered significant.

Results & Conclusions

We anticipate the incidence of granulation tissue at our institution will be higher than reported in the literature, and associated with factors such as improperly sized devices and subsequent leakage.

Funded By: Faculty of Medicine & Dentistry: Dr. ME Ledingham Memorial Summer Research Award

Abstract #: 92
Presenter: Claudine Thereza-Bussolaro
Supervisor: Carlos Floes Mir
Title: Forsus© Fixed Hybrid Appliance and Intermaxillary Elastics Effects on Airway Volume
Authors: Claudine Thereza-Bussolaro, Hee Soo Oh, Carlos Flores Mir, Manuel Lagravere
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: A link between Class II and pharyngeal airway(PA) dimensions has been reported. Forsus© Resistance Fatigue (FRF) and intermaxillary elastic (IM) has been reported as effective approaches for Class II malocclusion's treatment.

Objectives: Determine PA dimensions changes in Class II malocclusion patients treated with FRF or with IM.

Methods: 29 Class II malocclusion patients with average age of 12.7 years were included in this study (11 males and 18 females) The sample was divided into two groups (group 1: IM and group 2: FRF). CBCT's scans before (T1) and after treatment (T2) were obtained. Dolphin software was used to segment the oropharyngeal airway on all scans. Treatment duration time average was 1.07 years in Elastics and 1.79 years in Forsus©. Reliability was obtained using Intraclass Correlation Coefficient (ICC). Descriptive statistics, ANOVA, and paired t-test were used for analysis. University of Alberta ethical approval number MS3_Pro00057515. CBCTs were already available and were not taken specifically for this study.

Results: Reliability of the airway volume determination was excellent presenting an ICC score of >0.98.

IM group presented a PA increase between maximum 2.72% to 63.53%. The OA presented an increase of 17.72% to 95.68%.

FRF group presented a PA increase between 12% to 97.7%. The OA presented an increase of 29.1% to 106.9%.

Forsus© group showed a statistically significant difference between T1 and T2 in the PA while the elastic group did not ($p<0.05$). In the OA, IM group showed statistically significant difference while Forsus© did not.

There was no statistically significant difference between groups regarding PA ($p=0.39$) and OA ($p=0.91$).

Regarding gender, 90% of the males presented an increase of either PA or OA volume while only 38.89% of the females obtained upper airway effects.

Conclusions: Treatment with Forsus© and IM in Class II patients may increase the PA and OA volume. Between the two groups, FRF showed the highest change in both measured areas. Male patients showed a greater volume increase. A large variability was identified.

Funded By: WCHRI Trainee Travel Grant

Abstract #: 93
Presenter: Yong Zhang
Supervisor: Gregory Funk
Title: Towards an understanding of how ATP excites the brainstem inspiratory rhythm generator during hypoxia to reduce the hypoxic depression of breathing.
Authors: Yong Zhang, Vivian Biancardi, Ana Tapia, Toka Jaib, Alexander Gourine, Sergey Kasparov, Tucaaue Alvares, Gregory Funk
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: The ventilatory response to hypoxia comprises an initial increase in ventilation followed by a profound secondary depression, largely attributed to the inhibitory actions of adenosine in the brain, that can be life-threatening in premature infants (apnea of prematurity, AOP). Caffeine, an adenosine receptor antagonist, is used to treat AOP but has no effect in ~20% of infants. We have shown that ATP is released within the preBötzinger Complex (preBötC, critical site for inspiratory rhythm generation), during hypoxia where it acts via $P2Y_1$ receptors to attenuate this depression. Thus, there is great interest in understanding the mechanisms underlying this ATP-mediated excitation for its potential as an alternate means of stimulating breathing during hypoxia. The goal of my study was to test the hypothesis that $P2Y_1$ receptors excite breathing by elevating cAMP levels and potentiating the H-current in the membrane of preBötC inspiratory neurons.

Methods: I used an in-vitro model in which the preBötC is isolated in a brain slice and placed in a dish where it continues to generate inspiratory-related rhythm. Inspiratory network activity was recorded from XII nerves and the activity of inspiratory preBötC neurons was recorded via whole-cell recording. Effects of $P2Y_1$ agonists on network and neuronal activity were compared before and after addition of adenylyl cyclase or H-current antagonists.

Results: MRS2365 ($P2Y_1R$ agonist, 100 µM) evoked inward currents that reversed between -50 and -60 mV, consistent with activation of I_h in ~33% of inspiratoryneurons. MRS2365 also potentiated I_h by 32 ± 6% at -100 mV (n=8); induced a 6.6 mV depolarizing shift in the activation threshold (n=6). The MRS2365 inward current and its potentiation of I_h were blocked by ZD 7288 (open channel blocker of I_h, 100 µM). At the network level, pre-application of ZD 7288 at 100 µM (n=6) and 25 µM (n=10) attenuated the MRS2365-induced increase in inspiratory frequency by 94 ± 3% and 70 ± 12%, respectively. 15-min intracellular dialysis of SQ 22536 (adenylyl cyclase inhibitor, 100 µM) from the whole-cell pipette significantly attenuated the MRS2365 currents by 60 ± 4% (n = 9); SQ 22536 (100 µM) also attenuated the MRS2365-induced frequency increase by 67 ± 8% (n = 8).

Conclusion: These data suggest that the $P2Y_1R$-mediated excitation of the preBötC network is produced via a cAMP-dependent modulation of I_h in a subpopulation of inspiratory neurons, which could serve as a pharmaceutical target for treatment of AOP, especially in caffeine-insensitive infants.

Funded By: WCHRI Seed Grant; CIHR; Alberta Innovates; NSERC; CFI

women & children's health research institute

Abstract #: 94
Presenter: Victor Ezeugwu
Supervisor: Piush Mandhane
Title: Accelerometer-derived sleep duration, sedentary behaviour, and physical activity in preschoolers: The CHILD birth cohort study
Authors: Victor Ezeugwu, Valerie Carson, Sukhpreet Tamana, Stephen Hunter, Joyce Chikuma, Diana Lefebvre, Meghan Azad, Theo Moraes, CHILD Study Investigators, Piush Mandhane
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives: Movement behaviours, including sleep, sedentary behaviour (SB), and physical activity (PA), often interact to influence health outcomes. Movement behaviours develop in the early years and may track into adolescence and adulthood. We used data from a longitudinal birth cohort to describe the pattern of objectively-determined 24-hour movement behaviours in preschool children.

Methods/Approach: A sub-set of children (n=294, 54% boys) from the Edmonton site of the Canadian Healthy Infant Longitudinal Development (CHILD) study had movement behaviours assessed using the Actigraph GT3X-BT accelerometer. Participants wore the Actigraph on their non-dominant wrist for at least 4 days at ages three and five years. Minutes per day were derived for time spent in sleep (visual inspection of raw data), SB, light PA, and moderate-to-vigorous PA. The stability of movement behaviours over time was determined with Spearman-rank correlation as small (≤ 0.29), moderate (0.30 - 0.49), or large (≥0.5). Changes in movement behaviours between 3 and 5 years were tested using a three-level (age, sex, individual) mixed-effects model to account for repeated measures. Differences in behaviours by sex and daycare/pre-school/school attendance were examined using independent t-tests at each age.

Results/Findings: Higher levels of moderate-to-vigorous PA were recorded at age five years (64.4 minutes per day ± 1.5) than at age three years (41.2 min/day ± 1.4; p<0.01). Similarly, Light PA (341.4 min/day ± 3.2) and sedentary behaviour (370.6 min/day ± 4.0) were higher at age five compared to age three (327.7 ± 2.9 min/day and 355.6 min/day ± 3.7, respectively, p<0.01). Conversely, children at age five had shorter sleep duration (612.4 min/day ± 3.1) compared to age three (666.4 min/day ± 2.9; p<0.01). Tracking coefficients were large for moderate-to-vigorous PA (0.57), moderate for light PA (0.49) and SB (0.44), and small for sleep (0.22). Girls had 13.3 min/day higher LPA at age five (p=0.04) compared to boys. Moderate-to-vigorous PA was 8.8 min/day higher in children who attended daycare/preschool/school at five years of age (p=0.04) than in those who did not. Conversely at age three, PA at all intensities were higher in children who did not attend daycare/pre-school compared to those who attended; p<0.01, while SB was higher (37.9 min/day ± 16.7) among attendees of daycare/pre-school compared to those who did not attend; p=0.02.

Conclusions: Preschool children slept less and became more active between 3 and 5 years of age, engaging in both PA. The child's location affects PA levels. PA at all intensities and SB were stable at moderate to large levels across the two time-points, underscoring a potential opportunity for early intervention.

Funded By: WCHRI Trainee Travel Grant; CIHR; Heart & Stroke Foundation; AllerGen

Abstract #: 95
Presenter: Nils Koch
Supervisor: Silvia Pagliardini
Title: Disinhibition of the pedunculopontine tegmental nucleus facilitates expiratory abdominal muscle activity
Authors: Nils Koch
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Respiration in the postnatal period of preterm and occasionally in full-term human infants is often characterized by frequent respiratory disturbances during sleep, particularly during rapid eye movement (REM) sleep. Preterm infants display a 3-5 times higher frequency in sleep-disordered breathing (SDB) compared to full term infants both in infancy and childhood. Therapies to treat SDB exist but efficacy and compliance are limited. Thus, understanding the modulatory control of breathing during sleep is a primary research priority for the development of alternate therapies. During breathing at rest, expiration is a passive process; however, expiratory muscles can be recruited under metabolic and respiratory distress to actively expel air and increase gas exchange. Our laboratory has also shown in rats that abdominal recruitment frequently occurs during REM sleep to decrease respiratory variability and increase tidal volume. As such, the process of active expiration is potentially an efficient and powerful option for increasing ventilation in respiratory disorders of central origin that mostly occur during sleep (apnea of prematurity, SDB, central and obstructive sleep apnea).The parafacial Respiratory Group (pFRG) in the medulla is responsible for the generation of active expiration in rats, and cholinergic excitation of this area induces recruitment of abdominal muscles and active expiration. The pFRG receives projections from numerous brainstem regions including the pedunculopontine tegmental nucleus (PPT) in the pons, an area that has been implicated in REM sleep generation and contains a population of cholinergic neurons. In this study we tested the hypothesis that PPT modulates pFRG activity and active expiration.

Methods

To test our hypothesis, we disinhibited the PPT by using bicuculline, a GABA-A antagonist, and recorded muscle activity from respiratory muscles (abdominal, diaphragm and genioglossus) as well as hippocampal EEG activity under urethane anesthesia.

Results

Disinhibition of PPT resulted in increased expiratory related abdominal activity associated with increased respiratory rate and decreased genioglossus inspiratory muscle activity. Additionally, increases in the duration of the activated (REM-like) state were observed during PPT disinhibition.

Conclusion

Our results suggest that the PPT plays a role in modulation of expiratory abdominal activity as well as in changes in brain states under urethane anesthesia.

Funded By: WCHRI Innovation Grant; Summer Studentship; CIHR; Natural Sciences and Engineering Research Council of Canada - Undergraduate Student Research Award

Abstract #: 96
Presenter: Felipe Ganz
Supervisor: Lesley Wiart
Title: The effectiveness of interventions to increase physical activity of children with physical disabilities: a systematic review.
Authors: Felipe Ganz, Shivangi Bajpai, Sana Amjad, Susan Armijo Olivo
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Increased sedentary behaviour and decreased physical activity is a concern in pediatric health care because of rising obesity rates and long-term adverse health effects. Since children with physical disabilities are even more sedentary than their peers without disabilities, there is a growing interest in increasing physical activity and decreasing sedentary behaviourin this group of children. The purpose of this systematic review was to review the evidence related to the effectiveness of interventions aimed to objectively increase physical activity and/or reduce sedentary behaviour in children with physical disabilities.

Methods: Six databases were searched to identify randomized controlled trials (RCTs) for this review. Articles were considered for inclusion if participants were aged 0–18 years, had physical disabilities, and the outcomes of interest were either physical activity and/or sedentary behaviour measured objectively. Two independent reviewers screened the abstracts found in the databases. Risk of bias was assessed using the Cochrane collaboration tool. Data were pooled considering mean differences with 95% confidence intervals.

Results: Nine articles were selected for inclusion. The majority of the studies implemented interventions in children with cerebral palsy (n=5). The remaining studies included children with other physical disabilities. Accelerometry was the most common objective measure of physical activity and sedentary behaviour. Overall, interventions targeted to increase physical activity and decrease sedentary behaviour did not demonstrate to be significantly better than absence of interventions in children with physical disabilities. Most of the studies were considered to be of unclear risk of bias.

Conclusion: There is limited evidence regarding interventions aimed to increase physical activity and decreased sedentary behaviour in children with physical disabilities. Future research should investigate these interventions and also considerinterventions that target behaviour change in a specific age range. In addition, interventions that addressed participation and increase physical activity in different environmental setting is necessary.

Funded By: WCHRI Trainee Travel Grant

Abstract #: 97
Presenter: Alexa Ferdinands
Supervisor: Kim Raine
Title: Building relationships in patient and community engagement through a community of practice
Authors: Alexa Ferdinands, Sabrina Lopresti, Kirstyn Morley
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Engaged research can enhance the meaningfulness of evidence produced for patients and community members. However, it can also pose challenges for novice researchers, such as overcoming barriers to collaborative processes, and navigating how to apply principles of engaged research in practice. As such, the Women and Children's Health Research Institute partnered with the Community-University Partnership for the Study of Children, Youth, and Families to develop a program supporting researchers' capacity for conducting engaged research regarding women and children's health. The purpose of this program (Patient and Community Engagement Training (PaCET)) is to create a community of practice (CoP) where researchers co-create learning by sharing knowledge, experiences, successes, and challenges. The CoP is structured around the current lived research experiences of its participants. Here, we discuss our experiences as CoP participants, focusing on lessons learned and implications for our research.

Methods: The CoP is a group of people who, through regular interaction, partake in learning around a shared interest. A CoP creates a dynamic, rich, and complex learning environment, recognizing that learning is a fundamentally social and relational process. PaCET provided a safe space for researchers to engage with facilitators in group discussions. Each researcher was in a different stage of their research projects, allowing for peer mentoring. Regular meetings over eight months, supplemented by in-person and email discussions, enabled opportunities for reflection on research decisions, values, and ethical principles.

Results: Through our CoP, we learned the significant value of building healthy relationships in engaged research. During the early stages of such projects, relationship-building contributes to trust between researchers, community members, and other stakeholders (e.g., funders), allowing for honest conversations where all partners' needs are understood and respected. However, we encountered several barriers to relationship-building, including competing priorities, paradigmatic differences, and limited resources. In our CoP, we recognized the need to establish these relationships well before a study is initiated, as well as to maintain conversations upon program completion to facilitate sustainability of program initiatives. The CoP also fostered relationships between colleagues in similar research fields which will last well beyond the scheduled eight-month period. Having such "critical friends" is extremely valuable for troubleshooting research challenges, and for celebrating successes.

Implications: In our collective experience, PaCET offered us as novice researchers a unique space for interdisciplinary discussions that enhanced our confidence and capacity to lead and participate in engaged research, both in the present and future.

Funded By: WCHRI Graduate Studentship; PaCET Award

Abstract #: 98
Presenter: Nitya Khetarpal
Supervisor: Sue Ross
Title: Recruiting to a ommunity-based participatory research (CBPR) study of aging Indigenous women's wellness: describing recruitment processes and outcome
Authors: Nitya Khetarpal, Sue Ross, Luwana Listener, Margaret Montour, Cora Voyageur
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

INTRODUCTION

In 2017, the Sohki Teyhew Group received CIHR funding to identify wellness strategies adopted by mature women as they age in the rural Indigenous community of Maskwacis. We describe our recruitment processes and outcomes for events held between June 2017 to July 2018.

METHODS

Data were abstracted from the minutes of 36 Sohki Teyhew Working Group(WG) and 2 Elders Advisory Committee (EAC) meetings: (1) To identify **recruitment processes**, abstracted text was entered into Excel and recruitment processes grouped into categories. (2) **Outcomes (event attendance)** were identified for the 2 community events and 3 Sharing Circles.

RESULTS

Recruitment strategies were similar for community events and Sharing Circles. ***Communication strategies*** included displaying posters throughout Maskwacis e.g. health centres and community noticeboards, Hawk Radio adverts and live-streaming of community events, Band newsletter adverts and reports. ***Tradition/culture*** was addressed by smudging meeting spaces, saying prayers, and inviting Elders to attend all events. ***Incentives*** were provided: a wholesome lunch, and prize draws of good food bags and/or gift cards. The ***setting*** was a shared gymnasium for the larger community events. Sharing Circles were held in smaller spaces in individual band/community settings to encourage women from different bands to attend. **Event attendance** was as follows**:** Menopause walk – 96 attendees, Aging Women's Wellness Workshop – 37, Sharing Circles – ranged from 9 to 23.

DISCUSSION

Recruitment exceeded Sohki Teyhew WG expectations for these events in Maskwacis. Recruitment strategies were expensive in time, effort and expense, but met their objectives to attract attendees. Similar strategies may be successful in other rural Indigenous communities but must be tailored for specific needs and expectations of individual communities.

Funded By: Mature Women's Health Research Cavarzan Chair

Abstract #: 99
Presenter: Harrison Anzinger
Supervisor: Lisa Hartling
Title: Making child health evidence usable to the public: what do parents want?
Authors: Harrison Anzinger, Sarah Elliott , Lisa Hartling
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Connecting parents to research evidence is known to improve health decision making. However, guidance on how to develop effective knowledge translation (KT) tools which synthesize child health evidence into a form understandable by parents is lacking. We conducted a comparative usability analysis of three KT tools to identify parent preferences and factors which influenced their usability.

Methods

We evaluated the usability of a Cochrane plain language summary (PLS), Cochrane blogshot, and a Systematic EvidEnce Disseminator (SEED) updated Wikipedia page on a child-health topic (Acute Otitis Media). Mixed method interviews involving a knowledge test, written questionnaire, and semi structured discussion were conducted with parents (n=16). Thematic analysis was used to synthesize the transcribed interviews.

Results

Parents preferred the blogshot over the PLS and Wikipedia page ($p=0.002$) and found the blogshot to be most aesthetic ($p=<0.001$), and easiest to use ($p=<0.001$). Knowledge questions and usability survey data also indicated the blogshot was the most preferred and effective KT tool.

Four key themes were derived from thematic analysis. Parents like KT tools that: 1) are simple, 2) are quick to access and use, 3) are trustworthy, and 4) inform how to manage the condition.

Conclusion

Out of the three KT tools assessed, blogshots were the most preferred by parents. It is important that child-health evidence be available in formats easily accessible and understandable by parents to improve decision-making, use of healthcare resources, and health outcomes. Further usability testing should be conducted involving broader populations and other conditions in order to generate guidelines to improve parent directed KT tools.

Funded By: Alberta Innovates Health Solutions (AIHS) Summer Studentship Award

Abstract #: 100
Presenter: Britt Voaklander
Supervisor: Maria Ospina
Title: The prevalence of diabetes in pregnancy among Indigenous women: A systematic review
Authors: Britt Voaklander, Stewart Rowe, Sandra Campbell, Dean Eurich, Maria Ospina
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction:

Diabetes in pregnancy, including both pre-existing diabetes and gestational diabetes mellitus (GDM), is a serious maternal morbidity that is associated with poor maternal and perinatal outcomes. These outcomes may include preeclampsia, caesarean section, preterm birth, macrosomia, as well an increased risk for the child to subsequently develop type 2 diabetes. Not every population reports the same burden of diabetes in pregnancy; in low-risk populations the prevalence is 2%, but among Indigenous women, the prevalence ranges from 3.1% to 12.8%. The purpose of this study is to synthesize the evidence on the burden of diabetes in pregnancy among Indigenous women and estimate the prevalence of both pre-existing and gestational diabetes mellitus.

Methods:

A study protocol was published on *Prospero: International Prospective Register of Systematic Review* (CRD42018095971), prior to the beginning of the study. Comprehensive searches of 9 biomedical electronic databases (from 1974 to May 2018) were conducted by an information specialist and supplemented by grey literature searches. Observational studies assessing the prevalence of diabetes (GDM and pre-existing) among Indigenous women compared to non-Indigenous women in Canada, Australia, the USA and New Zealand were included in the review. Two independent reviewers assessed study eligibility and evaluated the risk of bias of included studies using the Newcastle-Ottawa scale for cohort studies and Quality Assessment for Prevalence Studies for cross sectional studies.

Results:

Of the 1,292 citations identified, 32 studies met the inclusion criteria. Of the included studies 9 were from Australia, 9 from Canada, 14 from the USA and none from New Zealand. Data on the prevalence of pre-existing diabetes and GDM was reported in 14 studies, while 18 studies reported prevalence of GDM. The majority of studies used a cohort design (n=27) and of those most of them resulted in a risk of bias assessment of "unclear" (n=12). The most common risk of bias assessment for those studies that used a cross sectional design (n=5) was also "unclear" risk of bias (n=3). The prevalence of pre-existing diabetes ranged from 0.45%-3.9% among Indigenous women compared to 0.11%-1.2% among Non-Indigenous women. The prevalence of GDM among Indigenous women ranged between 1.3% - 11.4%, compared to 0.2%-7.5% for Non-Indigenous women.

Conclusion:

The preliminary analyses demonstrate that Indigenous women have a greater burden of diabetes in pregnancy. Future steps involve assessing the heterogeneity of the included studies for a meta-analysis.

Funded By: WCHRI Graduate Studentship; Indigenous Graduate Award and Metis Scholars Award

Abstract #: 101
Presenter: Cody Lewis
Supervisor: Gordon Chan
Title: Myt1 confers resistance to MK-1775 in breast cancer
Authors: Amirali Bukhari, Armin Gamper
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Entry into mitosis is independently regulated by two kinases, Wee1 and Myt1, which add inhibitory phosphates to the mitotic promoting factor Cdk1/cyclin B preventing mitosis during DNA replication or in the presence of damaged DNA. In *Drosophila* and *Xenopus* Wee1 and Myt1 exhibit functional redundancy; one kinase can compensate for the loss of the other. In human cancer cells, the loss of Wee1 (but not Myt1) is frequently reported to induce aberrant mitosis and cell death by mitotic catastrophe. This suggests that Wee1 (but not Myt1) is the essential Cdk1 inhibitor in human cells. MK-1775 is a selective Wee1 inhibitor that is currently in phase I/II clinical trials against different solid tumours including breast cancer. Well some tumours respond favourably to MK-1775, other tumours exhibit resistance. One reason tumours resist MK-1775 maybe due to the presence of Myt1, which can maintain Cdk1 inhibition in the absence of Wee1.

Methods: Myt1 expression was compared in normal breast tissue (n = 10) and breast tumour tissue (n = 179 patients) by cDNA microarray. Myt1 expression between tumour tissues was compared against tumour grade, overall survival, and disease-free survival. Cell survival in different cell lines (6 breast cancer, 2 normal breasts, and HeLa) was measured by crystal violet assay following treatment with MK-1775 in the presence of siRNA targeting Myt1 or scrambled. IC50 survival values were compared against Myt1 mRNA and protein levels. Live cell imaging was used to compared mitotic timing and cell death. Myt1 expression in the presence of MK-1775 was examined in vivo using MDA-MB-231 derived xenografts treated with 60 mg/kg MK-1775 or vehicle control for 23 days. IHC staining was used to compare Myt1 expression in tumours.

Results: Myt1 is overexpressed in breast cancer relative to normal breast tissue. High Myt1 expression in breast tumours is associated with a worse tumour grade and disease outcome. High Myt1 is associated with resistance to MK-1775. Resistant breast cancer cells have low Cdk1 activity relative to sensitive cell lines even in the presence of MK-1775. Treatment with MK-1775 over time induces Myt1 upregulation in both cell lines and tumour tissue in xenografts, suggesting a potential feedback loop for Cdk1 regulation. Knockdown of Myt1 enhances MK-1775 mediated cell killing by up to 7-fold in resistant breast cancer cells; cells prematurely enter and then arrest in mitosis, exhibit abnormally high Cdk1 activity (relative to MK-1775 treatment alone), and have double stranded DNA breaks that occur at the centromere.

Conclusions: Myt1 promotes resistance to MK-1775 in breast cancer cells through the inhibition of Cdk1 in the absence of Wee1 activity.

Funded By: NSERC

women & children's health research institute

Abstract #: 102
Presenter: Francisca Cristi Munoz
Supervisor: Maya Shmulevitz
Title: Combination of mutations to produce a more powerful oncolytic reovirus
Authors: Francisca Cristi Munoz, Wan Kong Yip, Mary Hitt, Maya Shmulevitz
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

BACKGROUND: Reovirus is a nonpathogenic virus that naturally inhabits the enteric tract of humans. Reovirus can also selectively infect and replicate in tumor cells and is therefore a candidate for cancer therapy undergoing clinical trials. A recent clinical trial found that patients with metastatic breast cancer treated with reovirus had a significant improvement in overall survival. However, there was not remission in these patients, indicating that reovirus therapy is promising but needs improvement. Given that wild-type reovirus (T3wt) is naturally adapted to enteric environments (rather than tumors), **I hypothesize that reovirus can be modified to infect tumor cells more efficiently**.

METHODS: By using site-directed mutagenesis and reverse genetics techniques I created mutant reoviruses with single or combined mutations. I evaluated plaque size of the mutants to reflect the proficiency of reovirus replication in tumor cells. I performed Western Blot analysis to evaluate viral protein levels.

RESULTS: Previously in the Shmulevitz lab we identified 24 possible oncolytic mutations. From these mutations, I identified eight that promote oncolysis. These mutations were abundant in the reovirus proteins sigma 1 (cell attachment) and lambda 2 (structural protein). Five of these eight mutations decrease sigma 1 protein levels which is a previously well described mechanism of increased oncolysis. Interestingly, three of the mutations generate the same sigma 1 levels as T3wt, suggesting a new mechanism of oncolysis. Then, I wondered if the combination of these oncolysis-promoting mutations could have additive effects on oncolysis. I found that the combination of mutations in sigma 1 and lambda 2 had additive effects on oncolysis, showing a 4-fold increase in plaque size relative to T3wt. Furthermore, the combination of the five best oncolytic mutations generated a super-virus that produced the biggest plaque size. Additionally, I have implemented an immunocompetent mouse model of breast cancer in which T3wt is able to reduce tumor growth. In the future, I will evaluate the oncolytic potency of the reovirus mutants in this breast cancer model and how they induce innate and adaptive anti-tumor immune responses.

CONCLUSIONS: My results show that it is possible to increase the oncolytic potency of wild-type reovirus and that the combination of mutations increases the oncolytic potency of T3wt *in vitro*.

IMPACT: My experiments will provide a better understanding of reovirus biology and how to improve reovirus as a cancer therapeutic. I hope my findings will eventually help the ~16,000 Albertans that live with cancer today.

Funded By: CIHR; Li Ka Shing Institute of Virology

Abstract #: 103
Presenter: Beate Sydora
Supervisor: Sue Ross
Title: Walking exercise as a symptom improvement therapy for women in menopause transition and postmenopausal: a scoping review
Authors: Beate Sydora, Cailey Turner, Alexandra Malley, Tami Shandro, Sue Ross
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

INTRODUCTION:

Menopause is a natural stage in every woman's life that is often accompanied with physical and psychosocial symptoms, along with a decrease in general well-being and an increased risk to health conditions such as osteoporosis and cardiovascular diseases. There is emerging evidence that exercise can greatly improve quality of life in menopausal women and significantly impact their general health; however, conclusive evidence is lacking.

Our objective was to conduct a scoping review of published literature to assess outcome of therapeutic walking programs for menopause symptoms and to identify features that have resulted in symptom improvements.

METHODS:

A literature search of six biomedical and exercise-related databases (Medline, EMBASE, CINAHL, Sport Discus, Scopus, and Web of Science) for articles published up to June 1, 2017 was completed with keywords related to menopause and walking. Data was collected into EndNote X8 reference manager to identify and remove duplicates. The final selection included all articles that studied walking as a health intervention for women in menopause transition or post-menopausal. Data was extracted and charted for publication year, author, participant characteristics, symptoms and health issues investigated, walking intervention specifics, and intervention results and outcomes. Relevant publications in foreign language were included and data were extracted with the help of colleagues native to the foreign language. Descriptive analysis was applied.

RESULTS:

3244 articles were collected from the six databases. After removing duplicates and applying inclusion and exclusion criteria 96 papers were charted for the final analysis. Studies described in the papers used a variety of designs; the majority were RCTs (44%) or studies using a before-after approach (41%). Studies included natural walking (n=87) and treadmill exercise (n=11). Specific outcomes included cardiovascular risk factors, (n=45), body weight (n=36), osteoporosis and bone markers (n=25), physical fitness (n=12), mental health (n=7), and sleep disorders (n=4) in addition to general menopause symptoms and menopause-related quality of life. Walking program duration was on average 2.7±1.1 hour/week (n=85) or 14.1±6.0 km/week (n=19) with an average weekly frequency of 3.7±1.0 (n=94). Overall, 92% of these studies showed a beneficial outcome in at least one medical category investigated.

CONCLUSION: Walking appears to have a positive impact on both body and mind in menopausal women and provides a widely accessible and inexpensive exercise to reduce symptoms and improve quality of life in midlife and postmenopausal.

SUPPORT: The study was funded by a WCHRI-CRISP grant, a WCHRI summer student grant to AM, and a summer student grant from the UoA Undergraduate Research Initiative awarded to CT.

Abstract #: 104
Presenter: Angela McBrien
Supervisor: Angela McBrien
Title: Fetal double outlet right ventricle: Diagnostic spectrum, associated extracardiac pathology and clinical outcomes
Authors: Anglea McBrien, Aisling Young, Kim Haberer, Oana Caluseria, Gayathri Wewala, Tim Colen, Luke Eckersley, Lisa Hornberger
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Double outlet right ventricle (DORV) is a heterogenous group of congenital heart defects (CHD) that is increasingly diagnosed prenatally. There is a paucity of data from the recent era regarding the diagnostic spectrum, extracardiac pathology, and clinical outcomes in DORV diagnosed in fetal life.

Methods: We examined all cases of fetal DORV diagnosed from 2007-2018.

Results: In the study period, 113 cases of fetal DORV were diagnosed at a mean gestational age (GA) of 23+/- 5 weeks (range 13-36 weeks). The majority of cases had a subaortic ventricular septal defect (VSD) (n= 61, 54%) with (n=50) or without (n=11) pulmonary outflow obstruction. The remainder had a subpulmonic VSD with transposed great arteries (n=29, 26%), a remote VSD with side-by-side great arteries (n=3, 3%), or DORV with left atrioventricular valve atresia (n=20, 18%). Of the 113, 103 (91%) had genetic testing which was normal in 68 (66%), including 33 with microarray. The remaining demonstrated trisomy 18 (n=12, 12%), trisomy 21 (n=3, 3%), trisomy 13 (n=3, 3%), triploidy (n=3, 3%), 22q11 microdeletion (n=3, 3%), and 1 each of trisomy 22, Turner's syndrome, Kabuki syndrome, Goldenhar syndrome, and unbalanced translocation of chromosome 17. There were 7 chromosomal anomalies of unknown significance identified on microarray (7%) and 1 microarray that identified an unknown combination of variants that was likely significant. Associations and syndromes identified clinically included heterotaxy (n=17, 15%), VACTERL (n=8, 8%), and CHARGE (n=2, 2%). With respect to clinical outcomes, pregnancy termination was chosen in 26 (23%) at a mean GA of 21+/-3 weeks. Intrauterine fetal demise (IUFD) occurred in 11 (10%) patients at a mean GA of 30+/-7 weeks. Seventy-six (67%) were live-born at a mean GA of 38+/-2 weeks. Of livebirths, death occurred in the neonatal period in 11 (14%). Presence of trisomy 13 or 18 and any genetic abnormality were significant predictors of IUFD (7/15 v 4/98, $p < 0.01$ and 9/47 v 2/56, $p < 0.01$), but not of termination or neonatal death.

Conclusion: There is a higher rate of genetic and syndromic abnormalities in this modern cohort of prenatally diagnosed DORV than has been previously reported. There is a high rate of termination, IUFD and neonatal death. The increased rate of IUFD with a genetic abnormality highlights the need for prenatal genetic testing. This data adds insight to prenatal counselling for DORV.

Abstract #: 105
Presenter: Tausha Prisnee
Supervisor: Benjamin Willing
Title: The effect of antibiotics on gastrointestinal yeast in neonatal piglets
Authors: Tausha Prisnee, Janelle Fouhse, Carla Sosa Alvarado, Natalie Diether, Benjamin Willing
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Alterations in the microbiome as a result of neonatal antibiotic exposure have been associated with adverse outcomes such as obesity, asthma, and allergies. We have previously shown in a piglet model that neonatal antibiotic exposure alters pancreatic islet cell development, impairs glucose metabolism later in life, and favors *Escherichia coli* colonization. The eukaryotic component of the microbiome (mycobiome) can flourish in response to antibiotics. However, changes in the mycobiome in response to antibiotics and the role in long-term health remains poorly characterized. Therefore, the objective of this study was to determine the effect of neonatal antibiotic exposure on the intestinal mycobiome and the relationship to changes in the bacterial community.

Methods

18 newborn sow-fed piglets from 3 litters were randomly assigned to placebo (PL), amoxicillin (AM), or amoxicillin plus clavulanic acid (AMC) groups. Piglets received treatments orally at 15 mg/kg twice daily from postnatal day (PND) 0 to 7 when they were terminated to collect cecal contents. Total yeast, coliforms, and bacteria were enumerated in cecal contents by plating on selective and non-selective media and real-time polymerase chain reaction (qPCR). Yeast isolates were identified via Sanger sequencing of the 26S rRNA gene.

Results

Live isolated yeast included *Candida albicans*, *Candida glabrata, Kazachstania slooffiae, and Pichia kudriavzevii,* with total counts ranging from undetectable to 10^6 colony forming units per g, and showed a pattern of increased abundance in response to AMC treatment in pigs from litters where yeast were cultivable. When enumerated via qPCR, total yeast was higher in AMC treated animals compared to PL ($P = 0.03$), with AM treatment showing intermediate abundance between control and AMC. This pattern was consistent in all litters of piglets, despite the lack of cultivable yeast in one of the litters. Total anaerobic bacteria and cecal coliforms were lower ($P = 0.02$ and $P = 0.01$, respectively) in AMC treated pigs compared to PL, but were not lower in AM treated pigs ($P > 0.05$).

Conclusions

Neonatal AMC administration has the ability to alter the gut mycobiome and may create an environment in which yeast can flourish due to a decrease in competitive microbes. The observed difference in plating versus qPCR data suggests that there is a component of the mycobiome that is not detected by our culture methods. The mycobiome responds to clinically relevant antibiotics in a neonatal piglet model and indicates that increases in yeast populations may contribute to the previously observed metabolic outcomes associated with antibiotic treatment.

Funded By: Alberta Agriculture and Forestry

Abstract #: 106
Presenter: Jiabo Guo
Supervisor: Denise Hemmings
Title: Lipid receptor imbalance in preeclampsia is attributed to high levels of tumor necrosis factor-α (TNF-α)
Authors: Jiabo Guo, Fakhr Yuliya, Kristin Huntley, Martina Mackova, Denise Hemmings
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Background: Preeclampsia (PE) is a hypertensive pregnancy disorder. Systemic inflammation is an attribute in PE due to the increased release of inflammatory cytokines into the maternal blood. TNF-α is an example of these cytokines. It damages placental health by affecting trophoblasts, the placental cells that regulate nutrient transfer and barrier function. TNF-α could be doing this by increasing the levels of Sphingosine 1-Phosphate Receptor 2 (S1PR2). This receptor is overabundant in the placentas of PE women and its activation by its ligand, Sphingosine-1-Phosphate, contributes to the systemic inflammation. TNF-α increases S1PR2 expression in endothelial cells. However, the effect of TNF-α on S1PR2 expression in trophoblasts is unknown.

Aims: To understand whether circulating levels of TNF-α alone lead to the significant elevation in S1PR2 expression observed in PE and thus target S1PR2 as an intermediary molecule to improve placental health since blocking TNF-α itself harms fetal development.

Hypothesis: TNF-α increases S1PR2 expression in a human term trophoblast cell line as well as trophoblasts isolated from human placentas at term. S1PR2 expression is higher in placentas of PE women compared to placentas from normal term pregnancies.

Methods: S1PR2 expression was quantified in total protein isolated from placental biopsies from normal (n=15) and PE (n=5) mothers by Western Blot (WB). Specific S1PR2 expression in trophoblasts was assessed by co-immunohistochemical staining (IHC) using cytokeratin 7 as a trophoblast marker. Cultured BeWo cells, a human term trophoblast cell line, and primary trophoblasts were exposed to 0-20ng/mL of TNF-α for 24 hrs and S1PR2 expression was assessed by Western blot and IHC.

Results: S1PR2 expression was higher in placental biopsies by 1.525+/- 0.556 fold (p=0.02) and trophoblasts from PE women. In BeWos, S1PR2 expression significantly decreased by 39+/-13.9% at 10ng/mL and 51.5+/-3.7% at 20 ng/mL of TNF-α(p=0.017) with WB. In primary trophoblasts, S1PR2 expression significantly increased by 116.7+/-6.9 % at 20ng/mL of TNF-α (p=0.0099) with IHC and by 200% at 20ng/mL with WB.

Conclusions: BeWos respond by reducing S1PR2 expression levels, contradicting our hypothesis and existing literature. Primary trophoblasts respond to TNF-α by increasing S1PR2 expression, supporting our hypothesis. Thus, BeWos are not an accurate model for studying S1PRs. S1PR2 expression is higher in placental lysates and particularly in trophoblasts of placentas from women with PE. Thus, exposure to TNF-α alone is sufficient to increase S1PR2 expression, observed in PE. We will now move to inhibiting S1PR2 to assess its function in overall placental health.

Funded By: WCHRI Summer Studentship

Abstract #: 107
Presenter: Shela Hirani
Supervisor: Solina Richter
Title: Maternal and Child Health During Forced Displacement
Authors: Shela Hirani, Solina Richter
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Geopolitical issues like natural disasters and armed conflicts not only adversely affect the progress and prosperity of a nation but also result in forced displacement among vulnerable populations. During forced displacement, the population at risk is forced to flee from their geographical area and seek refuge either in their own country as an internally displaced person, maintain a refugee status in another country, or seek an asylum outside their country without maintaining a refugee status. Although forced displacement intends to save lives, preserve well-being and recover the affected population, the potential and actual population health risks associated with it cannot be ignored. Jeopardized maternal and child health is one of the serious repercussions of forced displacement that results in an unexpected rise in mortality and morbidity among women and young children.

Objectives: This paper presents the effects of forced displacement on maternal and child health, highlights the major pitfalls in delivering humanitarian services to this vulnerable group, and underscores the need of multi-layered interventions to improve health, protect rights and reduce vulnerabilities during forced displacements.

Methods: A comprehensive literature search was undertaken from the databases including, MEDLINE, CINAHL, EBSCOhost, Google Scholar, Scopus, and ProQuest. No restrictions were placed on geographical region, type, and year of publication. The keywords used were: displacement, child, women, health, challenges, maladjustment, morbidity, cultural sensitivity, and interventions.

Findings: Forced displacement negatively affects maternal and child health. The key challenges during forced displacement include food insecurity, lack of shelter, non-availability of clean water and sanitation, the poor infrastructure of healthcare services, non-availability of birth attendants and healthcare professionals to tackle medical emergencies, inaccessibility to educational and training facilities, and lack of cultural sensitivity of humanitarian workers. The ultimate outcome of forced displacement is a sudden rise in maternal and child mortality and morbidity, maladjustment, psychological issues, altered familial roles, displaced parenting, and vulnerability to exploitation.

Conclusions: In view of Bronfenbrenner's socio-ecological framework (1979), multi-layered interventions are proposed to improve maternal and child health during forced displacements. These interventions include enhancing the resilience of the vulnerable population, creating women and child-friendly spaces, offering psycho-social supportive measures, offering preventive and curative health care services, building safe and healthy infrastructures, and providing gender and culturally sensitive care to promote the health of this vulnerable group.

Abstract #: 108
Presenter: Nataliia Hula
Supervisor: Sandra Davidge
Title: Effect of maternal antioxidant (nMitoQ) treatment on cardiac outcomes in a rat model of intrauterine growth restriction
Authors: Nataliia Hula, Amin Shah, Raven Kirschenman, Anita Quon, Floor Spaans, Tom Phillips, Patrick Case, Jude Morton, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Pregnancy complications associated with placental hypoxia/oxidative stress can lead to the development of intrauterine growth restriction (IUGR). IUGR offspring may experience cardiovascular complications in adult life. We previously revealed that the hearts of adult IUGR offspring are more susceptible to ischemia/reperfusion (I/R) injury. Therefore, we have been testing early intervention strategies to improve fetal outcomes. Our strategy has been testing whether treating the placenta with nMitoQ, a mitochondrial antioxidant linked to nanoparticles for specific localization to the placenta, will improve placenta function and, ultimately, fetal outcomes. Previously, maternal nMitoQ treatment improved vascular function in male and female adult IUGR offspring, and decreased oxidative stress in female fetal IUGR hearts on gestational day (GD) 21. The impact of maternal nMitoQ on cardiac function in adult IUGR offspring is not known. We hypothesized that maternal nMitoQ treatment would reduce the susceptibility of cardiac I/R injury in female IUGR offspring.

Methods

Pregnant Sprague-Dawley rats were randomized into normoxic (21% O_2) and hypoxic (11% O_2) groups from GD15 to GD21 and intravenously injected with saline or nMitoQ (125 µM) on GD15. On postnatal day (PD) 1, PD 21 and 4-month, biometrics of the offspring were recorded. In 4 months old offspring, blood pressure and susceptibility to I/R injury was measured using tail-cuff plethysmography and *ex vivo* isolated working heart technique, respectively.

Results

Hypoxia tended to decrease neonatal female (p=0.066) and male (p=0.088) weights. nMitoQ treatment did not affect neonatal weight on PD1, while on PD21 there was an interaction between nMitoQ treatment and hypoxia (p=0.01) in female body weight. However, at 4-months of age, weight was not different. Neither prenatal hypoxic exposure nor nMitoQ treatment had an effect on blood pressure of adult 4-month old offspring (n=2-3). Contrary to our previous studies, prenatal hypoxia did not alter the heart capacity to recover from 20 min no flow ischemic insult in female offspring compare to controls (percent recovery from baseline: 78.39±8.36% vs 86.09±8.49%; ns). nMitoQ treatment had no effects.

Conclusion

In this pilot study, our preliminary data did not achieve a phenotype to assess the impact of nMitoQ treatment. Notably, 20 min of ischemia did not reduce cardiac function in offspring from hypoxic pregnancies. However, further studies will be necessary to increase n-numbers and extend ischemia time to 30 min. These data contribute to our understanding of the nMitoQ treatment effect in pregnancies complicated by hypoxia on the development of cardiovascular diseases later in life.

Funded By: WCHRI Start-up or Retention Funding; CIHR; Stefan and Pelagia Wychowanec Graduate Scholarship

women & children's health research institute

Abstract #: 109
Presenter: Nayara Lopes
Supervisor: David Olson
Title: Social isolation predisposes rats to adverse pregnancy outcomes and altered stress markers
Authors: Nayara Lopes, Vaishvi Patel, Ashlee Matkin, Keiko McCreary, Xin Fang, Erin Falkenberg, Gerlinde Metz, David Olson
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Maternal stress before and during pregnancy results in adverse perinatal outcomes, such as preterm labour, which predisposes to metabolic syndrome and cardiovascular diseases. Social isolation (SI) is considered a chronic stress and is associated with altered brain development and behaviour in rodents. SI may help model the adverse pregnancy outcomes (APOs) associated with depression in pregnant women. We hypothesize that a period of SI before conception predisposes a rat to APOs and to an altered profile of stress markers that can be epigenetically inherited.

Methods: Female Long-Evans rats (F0, n=8-10) were assigned to SI or control groups. SI was implemented by housing the female rats alone for two weeks starting at 12-weeks-old, followed by pairing with a male for breeding. Gestational age at birth was recorded and dams were kept with pups until normal weaning age when uterine tissues were collected. The following generations (F1-F3, n=8-10) were divided into three groups: control (2-3 housed together), transgenerational (F0 stressed only) and multigenerational (stress in each generation). RT-qPCR was used to quantify mRNA abundance for uterine stress markers such as pro-inflammatory mediators (*IL1b, IL1a, IL6, IL10*) and their receptors, corticotropin-releasing hormone and its receptors (*Crh, Crhr1/2)* as well as 11β-hydroxysteroid dehydrogenase type2 *(Hsd11b2).* Data was analyzed in Prism by t-test, $p<0.05$.

Results: Preliminary results showed that SI tends to upregulate proinflammatory gene expression in uterine tissues of F0 dams, however the changes were not significant. ***IL1β*** mRNA was 1.5x increased in the SI group compared to controls. We see an increasing trend for ***IL1α*** and ***IL10*** in SI group. ***IL1Ra*** mRNA levels were 1.5 times higher in SI group, similar to previous findings in placenta of preeclamptic women. However, ***IL6*** was the only proinflammatory cytokine that was downregulated in SI group. Opposed to what we expected, in F0 dams, ***CRH*** mRNA expression was significantly decreased in SI group (p=0.012), whereas ***CRHR1*** mRNA was decreased and ***CRHR2*** increased in SI group (p>0.05). Lastly, ***HSD2*** mRNA levels were significantly increased in SI group (p=0.026), possibly leading to higher levels of corticosterone reaching the fetuses.

Conclusions: We showed that SI slightly modified stress markers in the F0 generation, yet the analysis of the next generations (F1-F3) will help us to establish the effects of SI preceding pregnancy. Our results support the concept of adaptation to a stressful environment, but future analysis of the multi/transgenerational groups will explain the impacts of SI throughout the generations.

Funded By: CIHR

women & children's health research institute

Abstract #: 110
Presenter: Floor Spaans
Supervisor: Sandra Davidge
Title: Effects of syncytiotrophoblast extracellular vesicles on angiotensin II-induced vasoconstriction in uterine arteries from LOX-1 overexpressing mice
Authors: Floor Spaans, Jude Morton, Raven Kirschenman, Tatsuya Sawamura, Dionne Tannetta, Ian Sargent, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Placental factors, such as syncytiotrophoblast extracellular vesicles (STBEVs) have been suggested to contribute to maternal vascular dysfunction in women with preeclampsia (PE). Increased levels of STBEVs have been found in women with PE and they have been shown to disturb endothelial function *in vitro*, however, the mechanisms for the contribution of STBEVs to vascular dysfunction in PE are unknown. The lectin-like oxidized LDL receptor-1 (LOX-1) is a multi-ligand scavenger receptor expressed on endothelial cells. Increased LOX-1 activation is associated with vascular dysfunction; and LOX-1 expression is increased in women with PE. Recently, LOX-1 has been shown to interact with angiotensin II type 1 receptor (AT-1) signaling. We hypothesized that STBEVs could be LOX-1 ligands and could contribute to angiotensin II (Ang II)-mediated vascular dysfunction by LOX-1 activation.

Methods

Uterine arteries were isolated from WT (-/-) controls or LOX-1 overexpressing mice (LOX-1OE; carrying bovine LOX-1 transgene) on gestational day 18 (term is day 19) and were incubated overnight with or without STBEVs (200 mg/ml). Vasoconstriction responses to Ang II were assessed using wire myography. The specific role of AT-1 and LOX-1 was analyzed using the AT-1 receptor inhibitor candesartan or the LOX-1 ligand, oxidized LDL (oxLDL).

Results

Vasoconstriction responses to Ang II were reduced by STBEV-incubation in arteries from WT but not LOX-1OE mice (AUC: 6.18±0.47 WT control vs. 3.7±0.90 WT STBEVs; $p<0.05$). Responses to Ang II were completely inhibited by AT-1 receptor blocking in all groups. oxLDL did not have any effects in uterine arteries from WT mice. However, in LOX-1OE mice, an interaction ($p=0.019$) was observed between STBEV-incubation and oxLDL stimulation, with oxLDL reducing the response in control arteries while increasing Ang II responses in STBEV-incubated arteries.

Conclusions

In conditions of normal LOX-1 expression (i.e. normal pregnancy), STBEVs could contribute to the normal reduction in Ang II responsiveness that is observed during pregnancy. However, in conditions of increased LOX-1 expression (such as in women with PE), activation of LOX-1 increases the responsiveness to Ang II during pregnancy, but only in the presence of STBEVs. Together, these data suggest that both higher LOX-1 expression together with increased levels of STBEVs during gestation could contribute to vascular complications in pregnancy, such as observed in women with PE. These data increase our understanding of endothelial dysfunction in PE and contribute to the development of novel treatment strategies in the future.

Funded By: WCHRI Start-up or Retention Funding; CIHR; Alberta Innovates; Molly Towell Perinatal Research Foundation

Abstract #: 111
Presenter: Shawna Stafford
Supervisor: Helen Steed
Title: Managing women with obesity at term: The scope of practice in the absence of a guideline.
Authors: Shawna Stafford, Ashley Demsky, Richard Oster, Daniel Birch, Helen Steed
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction/Objectives: It is estimated that approximately one third of Canadians are obese. During pregnancy, obesity is associated with numerous adverse maternal and fetal outcomes. Currently, there are no available clinical practice guidelines that establish the standard of care for women with obesity at term pregnancy. This results in obstetricians using a wide array of approaches and interventions as they care for an increasing number of patients with obesity. These interventions carry a risk of increasing maternal and fetal morbidity. The objective of this study is to explore the different approaches to the pregnant patient with obesity at term to identify key gaps in knowledge generation and dissemination.

Methods/Approach: To understand how obesity affects obstetrician's management of women at term pregnancy, we are using a mixed method approach. Concept mapping provides a visual representation of a participant's knowledge about how obesity affects their management of women at term. Seven obstetricians participated in independent concept mapping sessions. Resulting maps were analysed thematically and themes/subthemes were then used to design a survey revealing the current practice patterns for the management of women with obesity at term.

Results: Overall, seven dominant themes emerged from our thematic analysis:

1. Obstetricians define obesity differently. While some use quantitative measures like pre-pregnancy weight or BMI, others rely on general physical appearance to assess whether patients have obesity.
2. Communication with patients should be "direct" and "honest". Openly discussing the medical implications of obesity can help patients understand the importance of achieving a healthy weight in pregnancy.
3. Understanding fetal wellbeing is more challenging in patients with obesity in both the pre-natal and intrapartum period.
4. Obstetricians recommend induction of labour for large for gestational age (LGA) fetuses but not maternal obesity.
5. Women with obesity have abnormal labour.
6. Obstetricians expect more complications, alter their surgical approach, and adjust their threshold for cesarean deliveries in patients with obesity.
7. Education and knowledge translation about obesity in pregnancy is inadequate.

Conclusions: Obesity affects an obstetrician's management of women in pregnancy. By surveying clinicians, we will gain broader insights into the full scope of practice for women with obesity at term. Using information gathered from obstetricians, the most pertinent evidence for clinical decision making can be identified and assembled into up-to-date and easy to access clinical guidelines. With improved knowledge dissemination, obstetricians will be better equipped to provide evidence based and consistent care to women with obesity at term.

Funded By: WCHRI Support services

Abstract #: 112
Presenter: Deborah Adesegun
Supervisor: Margie H Davenport., Radha Chari
Title: Prenatal exercise and pre-gestational diseases: a systematic review and meta-analysis
Authors: Deborah Adesegun, Chenxi Cai, Allison Sivak, Margie H. Davenport, Radha Chari
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

OBJECTIVE: To examine the effect of prenatal exercise on birth outcomes in women with pre-gestational diseases including chronic hypertension, type 1 diabetes and type 2 diabetes.

DATA SOURCES: A structured search of online databases up to June 8, 2018.

METHODS OF STUDY SELECTION: Studies of all designs and languages were included if they contained information on the Population (pregnant women with pre-gestational diseases), Intervention (subjective or objective measures of frequency, intensity, duration, volume or type of exercise), Comparator (no exercise or different frequency, intensity, duration, volume or type of exercise), and Outcome (birthweight, macrosomia [birthweight >4000 g], large for gestational age [LGA], low birth weight [<2500g], small for gestational age [<10th percentile], APGAR, pre-term birth [<37 weeks], cesarean section, preeclampsia, and glycemic control).

TABULATIONS, INTEGRATION, AND RESULTS: A total of five studies (n=221 women) were included. "Low" to "very low" quality evidence revealed that prenatal exercise reduced the odds of caesarean delivery by 55% in women with T1DM and CH (OR 0.45, 95% confidence interval [CI] 0.22, 0.95, I^2= 0%). The odds of low (<2500g) or high birthweight (>4000g), Apgar score at 1 minute and 5 minutes, pre-eclampsia, and preterm birth were not different between women who exercised with those who did not.

CONCLUSION: Prenatal exercise reduced the odds of cesarean section, and did not increase the risk of adverse maternal or neonatal outcomes.

Funded By: Radha Chari/AHS

women & children's health research institute

Abstract #: 113
Presenter: Gayathri Wewala
Supervisor: Lisa Hornberger
Title: Exploring the cardiovascular health of preteen and teenage children of diabetic mothers: Evidence of early cardiovascular programming
Authors: Gayathri Wewala, Victor Do, Lily Lin, Edmond Ryan, Tammy McNab, Luke Eckersley, Michael Stickland, Sandra Davidge, Winnie Savard, Lisa K Hornberger
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Children of diabetic mothers (CDM) are at an increased risk for adult cardiovascular disease (CVD). We have previously demonstrated that CDMs have persistent left ventricular (LV) thickness and aortic stiffness from late infancy to early childhood. These findings led us to study the cardiovascular health of an independent cohort of preteens/early teens of diabetic mothers. We hypothesized that CDMs aged 9-16 years will have increased LV thickness and aortic stiffness in comparison to aged-matched controls.

Methods

We prospectively recruited 9-16 year old CDM of mothers with a history of pre-gestational (type 1) diabetes and age matched healthy children of healthy mothers to participate. Their height, weight, and blood pressure (average of 3 measures) were recorded. A full structural and functional echocardiogram was performed to assess measures of LV wall thickness and systolic, diastolic and global function. Blood vessel reactivity was assessed non-invasively using the VENDYS system and aortic and peripheral arterial stiffness (pulse wave velocity, PWV) were measured by Doppler at echocardiography. Participants completed a 3-day diet log, HAES physical activity questionnaire, survey of family history, and wore an activity monitor for 1 week. Offline analysis of the echocardiograms was completed with a focus on LV thickness, diastolic function and PWV.

Results

To date, 13 CDMs and 7 children from healthy pregnancies completed assessments. There was no difference in mean age, body surface area, and blood pressure between groups. Preliminary analysis showed no difference in LV thickness and blood vessel reactivity. Compared to controls, CDMs had evidence of increased aortic (PWV 3.6±0.4 m/s versus 2.5±0.2 m/s, p=0.0006) and peripheral arterial stiffness (PWV 7.1±0.6 m/s versus 6.3±0.6 m/s, p=0.007). Although LV free wall and septal wall thickness and measures of systolic and diastolic function did not differ, LV Tei index, a measure of global function, was increased in CDMs relative to controls (0.4±0.05 versus 0.3±0.02, respectively, p=0.03). The contributions of diet and physical activity level to these findings are currently being explored in a larger cohort.

Conclusion

Our preliminary data suggests preteens/early teens of type 1 diabetic mothers have increased aortic and peripheral arterial stiffness and show a difference in global left ventricular function, findings that may contribute long-term to adult cardiovascular disease.

Funded By: WCHRI Summer Studentship; Alberta Innovates

Abstract #: 114
Presenter: Ghazal Babolmorad
Supervisor: Amit Bhavsar
Title: Understanding the functional pharmacogenomics of cisplatin induced ototoxicity to reduce its occurrence.
Authors: Ghazal Babolmorad, Ivan Kristell Domingo, Amit Bhavsar
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Cisplatin is a chemotherapeutic used in cancer patients to treat solid tumors. However, cisplatin usage is limited due to possible irreversible adverse drug reactions, including ototoxicity which manifests as permanent hearing loss. A genome wide association study (GWAS) in patients treated for childhood cancer identified associations of cisplatin ototoxicity with genetic variations in the innate immune receptor, TLR4, which protected carriers against the development of cisplatin induced hearing loss. We were trying to understand the role of TLR4 signaling pathways in cisplatin ototoxicity in a murine Organ of Corti cell-based model. The **specific objectives** of this study were to: 1) block TLR4 signaling using TLR4 inhibitors and examine cisplatin "ototoxicity" *in vitro*; 2) create a *TLR4* deletion in an *in vitro* hair cell model; 3) confirm the loss of *TLR4* through genetic, and functional analyses; and 4) examine the impact of *TLR4* deletion on cisplatin "ototoxicity" *in vitro*.

Methods: Murine embryonic inner ear cell line HEI-OC1 was used as an *in vitro* model to study cisplatin "ototoxicity". To meet **objective 1**, TLR4 signaling was blocked using TAK 242 inhibitor. To meet **objective 2,** CRISPR/Cas9 genome-editing technology was used to disrupt the *Tlr4* gene in HEI-OC1 cells. Genomic cleavage efficiency was quantified using an assay that specifically cleaves mismatched DNA in the targeted *Tlr4* locus. To meet **objective 3**, single clones of genome-edited HEI-OC1 cells were isolated. Genome-edited cells that lack TLR4 protein activity were Sanger sequenced at the *TLR4* locus to identify the nature of the genome edit. Finally, to meet objective 4, cisplatin "ototoxicity" responses were compared between *Tlr4*-deleted, negative controls and wild type HEI-OC1 cells.

Results:

Our preliminary results indicated that 1µM TAK242 has a rescue effect on HEI-OC1 cells treated with 20 µM cisplatin. Treatment with cisplatin significantly reduced HEI-OC1 cell viability and increased the expression of *IL-6*. CRISPR/Cas9 cleavage efficiency was estimated at 15%. Sanger sequencing results confirmed farm-shift mutation in in exon 1 of Tlr4. MTT analyses indicated that genome-edited HEI-OC1 cells are more stable than negative controls.

Conclusion:

- Identification of a new pathway (TLR4) that contributes to the development of cisplatin ototoxicity.
- Cisplatin ototoxicity decreased in blocked TLR4 signaling pathway cells and in genome-edited HEI-OC1 cells.

Funded By: WCHRI Graduate Studentship; CIHR

Abstract #: 115
Presenter: Kaitlyn Lopushinsky
Supervisor: Loretta Fiorillo
Title: Ice, Ice, Baby: Pitfalls of ice bag application for neonatal supraventricular tachycardia conversion
Authors: Kaitlyn Lopushinsky, Loretta Fiorillo
Affiliations: Other
Research Activity: Children's Health and Well-Being

Introduction

Supraventricular tachycardia (SVT) is a common neonatal condition of which most cases resolve in infancy. One of the vagal maneuvers used to convert SVT episodes is application of ice or cold water to a patient's face, stimulating the diving reflex. One complication of this treatment in neonates is the development of cold panniculitis of the exposed area, due to increased fat pad size and saturated fatty acid content in neonates.

Methods

The case of a 10-day-old female who developed discrete nodules of cold panniculitis on her face after application of ice bags for SVT conversion is described. A concise literature review is also provided regarding neonatal cold panniculitis in context of ice bag treatment for cardiac arrhythmia.

Results

During episodes of SVT, the patient was often treated with ice bags to her face to induce the diving reflex and terminate the tachycardia. At 10-days of age, 4 erythematous nodules were noted on the face, 3 on the left cheek and 1 on the right forehead. The application of ice bags was stopped and her SVT was subsequently treated with oral propranolol and flecainide. Our patient also had hypercalcemia and thrombocytosis at the time of presentation of cutaneous findings which have not yet been linked to cold panniculitis. The nodules resolved within days and were not biopsied. A concise literature review is also provided regarding neonatal cold panniculitis in context of ice bag treatment for cardiac arrhythmia.

Conclusions

Our case emphasizes the importance of recognizing cold panniculitis, and its possible association with increased platelet and calcium levels, for appropriate patient management. This case also points to a relative contraindication of application of ice to the face of a newborn. Other methods to stimulate the vagal nerve, such as insertion of a nasogastric tube could be employed instead for SVT conversion. Pharmacological treatments including adenosine should be used more promptly for terminating neonatal SVT rather than application of ice to the face. This case provides both clinical example and scientific review to aid the audience in management decisions for neonatal supraventricular tachycardia.

Abstract #: 116
Presenter: Fatemeh Ramazani
Supervisor: Hamdy El-Hakim
Title: Side effects and complications of injection laryngoplasty for treatment of type one laryngeal clefts
Authors: Fatemeh Ramazani , Andre Isaac, Hamdy El-Hakim
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Type 1 laryngeal clefts (LC1) are claimed to be commonly associated with swallowing dysfunction (SD) in children. The management modalities for this condition include conservative approach, endoscopic repair, and injection laryngoplasty (IL). There remains ongoing controversy regarding the best treatment approach. Proponents of IL argue the case for a minimally invasive, brief procedure involving injection of a biologically friendly product such as sodium carboxymethylcellulose gel, hydrated porcine gelatin powder, hyaluronic acid derivatives, or autologous fat into the interarytenoid space to augment it. Despite reports showing promising success rates, potential complications have never been reported or systematically assessed.

Methodology

This retrospective chart review was set at the University of Alberta Stollery Children's Hospital. Participants included pediatric patients who had undergone IL for treatment of LC1. Patients were identified from the surgical log of the Pediatric Otolaryngologist. Pediatric patients with a diagnosis of endoscopy proven LC1 treated with IL between 2000 and 2018 were included in this study. Patients with concurrent airway anomalies or other procedures were excluded. Charts were reviewed for demographics (age and gender), as well as concurrent medical diagnoses, procedures performed, type of injected material, and complications within the first 14 post-operative days including recovery room. Post-operative complications assessed were: respiratory distress requiring medical treatment (systemic or inhaled steroids, inhaled adrenaline, admission, and/or repeat endoscopy by bedside or under general anesthesia and surgical intervention).

Results

A total of 88 patients met the inclusion criteria for this study (53 males, 35 females). The mean age at which IL was performed was 33.15 months (SD= 23.2; range= 1-132 months). Of these patients, 8.0% experienced post-operative stridor (n=7), one experienced respiratory distress, and 4.5% (n=4) experienced a croup-like cough. For management of these symptoms, three patients required admission to hospital and one required medical management with systemic steroids and inhaled adrenaline. Only one case required admission to intensive care, endoscopic drainage of seroma, intubation and a course of systemic steroids.

Conclusion

IL for management of LC1 in the children may be associated with immediate post-operative complications in a small percentage of patients and the parents should be counselled appropriately. The record of some of these injectable agents demonstrate an incidence of tissue reaction in cosmetic surgery and it is likely that our estimate is on the low side given the design of our work.

Abstract #: 117
Presenter: Hafsa Riaz
Supervisor: Dawei Zhang
Title: Diagnosis of ABCB11 gene variations in children with progressive familial intrahepatic cholestasis (PFIC) type 2 in Pakistani cohort
Authors: Hafsa Riaz, Yasir Zahoor, Huma Arshad, Bixia Zheng, Dawei Zhang
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Progressive familial intrahepatic cholestasis (PFIC) begins in childhood and is associated with impaired bile secretion, leading to liver dysfunction. PFIC is an autosomal recessive disorder, presents with symptoms secondary to hepatic failure. The symptoms include jaundice with severe pruritus, yellow stool, and maybe hepatosplenomegaly. Bile salt export protein (BSEP) regulates flow of bile from hepatocytes. Genetic variations in ABCB11 gene are the cause of PFIC type 2. Such patients develop end stage liver disease and need to undergo liver transplantation before they reach to adolescence. Currently no data available on genetic variations in Pakistani patients with PFIC.

Methods

Blood samples were collected from 40 suspected PFIC patients from Children Hospital Lahore, Pakistan. Patients belong to different regions of Pakistan and different ethnic groups. 38 cases belong to consanguineous marriages, while two cases were from non-consanguineous marriages. Samples were taken after consents of patients' families.

Diagnosis for PFIC2 was made by comprehensive analysis of clinical features and genetic analysis. All coding exons were amplified by polymerase chain reaction and products were used to detect mutations in ABCB11 gene by sequencing. Sequencing variations were further analyzed in various available genomic databases including ExAC, HGMD and 1000 genome browsers.

Results

A total of 15 variations in ABCB11 were identified among 40 children with PFIC from Pakistan. Eight were homozygous while seven heterozygous. One variation c.3382C>T was identified among 3 children with two homozygous patterns and one heterozygous pattern. Out of 15, there were 8 novel variations, one nonsense mutation, one likely benign mutation.

Conclusion

Fifteen ABCB11 gene variations including eight novel mutations were identified among almost one third of PFIC children of Pakistani population. Other two third with no variation in ABCB11 may have variations in ATP8B1 or in intronic and promoter regions of these genes.

Funded By: Higher Education Commission Pakistan

Abstract #: 118
Presenter: Colin Lloyd
Supervisor: Linda Chui
Title: Clostridium difficile molecular epidemiology in a prospective cohort of Canadian children compared with cases of C. difficile infection
Authors: Colin Lloyd, Brendon Parsons, Tim Du, George Golding, Bonita Lee, Xiaoli Pang, Stephen Freedman, Linda Chui
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: *Clostridium difficile* is a toxin producing bacterium that commonly colonizes young children. We hypothesized that such carriage serves as a potential reservoir for toxigenic strains. In this study, we sought to determine the genetic relatedness of *C. difficile* among four populations: pediatric outpatients with symptoms of acute gastroenteritis (AGE), pediatric outpatients without AGE symptoms, and pediatric and adult inpatients with *C. difficile* infection (CDI). Additionally, we compared *C. difficile* toxin production between pediatric outpatients with and without AGE.

Methods: Pediatric outpatients were recruited through the APPETITE study from the Alberta Children's Hospital & Stollery Children's Hospital emergency departments, Thornhill Community Health Center, and Health Link Alberta. These samples tested positive for *C. difficile* toxin genes using the Luminex xTAG® Gastrointestinal Pathogen Panel. Inpatient samples tested positive for *C. difficile* toxin or toxin genes using either the C. DIFF QUIK CHEK COMPLETE® enzyme immunoassay (EIA) or Cepheid GeneXpert® *C. difficile* PCR assay. Inpatient cases were reviewed by Infection Prevention and Control and fulfilled CDI criteria. All samples were cultured for *C. difficile* and isolates tested for *tcdA, tcdB and cdtB* genes by PCR and genotyped using PCR ribotyping and pulsed-field gel electrophoresis (PFGE). Presence of *C. difficile* toxins in a subset of stool samples from pediatric outpatients with and without AGE was determined using EIA.

Results: A total of 173 *C. difficile* isolates from 97 inpatients (79 adult and 18 children) and 76 pediatric outpatients (59 with AGE and 17 without AGE) were included. Among 94 isolates from the pediatric population, ribotype 106 was predominant (21/76, 27.6% outpatients; 5/18; 27.8% inpatients) and ribotype 027 was predominant in the adults (35/79, 44.3%). Nineteen ribotypes were shared (137/173, 79.2%) among the two groups and sixteen unique ribotype and PFGE combinations (84/173, 48.6%) were also shared. Toxin gene profiles were similar between the pediatric and adult patients. Adult inpatients had a higher percentage of *cdtB* positive isolates (42/79, 53.2%) compared to pediatric outpatients (3/76, 3.95%) and pediatric inpatients (0/18, 0%), ($p<0.001$, chi square). The proportion of pediatric outpatients positive for *C. difficile* toxin was similar between those with (28/45, 62.2%) and without AGE (6/14, 42.9%) ($p=0.2$, chi-square).

Conclusion: A similar *C. difficile* toxin positivity rate between pediatric outpatients with and without AGE questions the role of *C. difficile* in childhood AGE. *C. difficile* strains found in adults were also identified in children; however, the underlying factors for causing disease in children are unclear.

Funded By: WCHRI Trainee Travel Grant; Alberta Innovates

Abstract #: 119
Presenter: Cara McLean
Supervisor: Anita Kozyrskyj
Title: Medical interventions during birth and their impact on Clostridioides difficile (C.difficile) colonization in Canadian infants at 3 months of age
Authors: Cara A McLean, Radha S Chari, Bonita Lee, Meghan B. Azad and Allan B Becker, Piushkumar J Mandhane, Malcolm R Sears, Stuart E Turvey, Theo J. Moraes and Padmaja Subbarao, James A Scott and Anita L Kozyrskyj, CHILD Study Investigators
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Abstract

Introduction Medical interventions during childbirth are increasing, with caesarean section (CS) delivery far exceeding recommended rates. CS has been associated with gut dysbiosis in early life. Infants who bypass beneficial maternal bacterial inoculation during vaginal birth, have been found to be commonly colonized by opportunistic bacteria such as *Clostridioides difficile (C. difficile)*, but factors leading to colonization remain unknown. This study aimed to determine the impact of medical interventions during delivery and its impact on the colonization of *C. difficile* at 3 months of age.

Methods This was a prospective cohort study utilizing data on 1481 mother-infant pairs from the Edmonton, Winnipeg and Vancouver sites of the Canadian Healthy Infant Longitudinal Development (CHILD) population-based birth cohort. Birth method, birth interventions (i.e. anaesthetics and oxytocin-like drugs to stimulate labor which include oxytocin, carbetocin, prostaglandins), and maternal and infant covariates were collected from hospital charts or maternal questionnaires. *C. difficile* was detected in infant fecal samples collected at 3-4 months of age using quantitative polymerase chain reaction and classified as present/absent. Logistic regression models were run to determine whether birth mode was associated with *C. difficile* colonization, adjusted for covariates and stratified by medical interventions.

Results Colonization rates of *C. difficile* were 31% among infants at 3 months of age. In unadjusted analysis, the odds of colonization with *C. difficile* was significantly increased with emergency CS and elective CS compared to vaginal birth with no maternal intrapartum antibiotic prophylaxis (IAP) (OR 1.76, 95% CI: 1.27-2.44 p=0.001 and OR 1.55, 95% CI: 1.06-2.26 p=0.024, respectively). Following adjustment for maternal gravida status, birthweight, anaesthetic and oxytocin use during delivery, hospital length-of-stay, maternal ethnicity and age, prenatal depression, postnatal smoking and breastfeeding, the association remained significant for infants born by emergency CS (OR 1.70, 95% CI: 1.15-2.49 p=0.007). Oxytocin-like drugs were used in 46% of births for induction or augmentation, and their use was more than 2-fold higher in infants born by emergency CS. After stratification for oxytocin-like drugs, the increased risk of *C. difficile* in infants born by emergency CS compared to vaginal birth with no IAP only remained significant for infants whose mothers received oxytocin-like drugs during delivery (aOR 2.0, 95% CI: 1.33-3.02 p=0.001).

Conclusions Caesarean section delivery, specifically in case of an emergency, is significantly associated with *C. difficile* colonization during infancy. Additionally, the use of oxytocin-like drugs during labour is another factor influencing colonization.

Funded By: CIHR

Abstract #: 120
Presenter: Aaron van der Leek
Supervisor: Dr. Anita Kozyrskyj
Title: Persistent Clostridioides difficile (C. difficile) in infants with low fecal immunoglobulin A concentrations
Authors:
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Evidence has been accumulating that early-life *Clostridioides difficile* (C. difficile) colonization of the gut is a marker for microbial dysbiosis and later development of atopic disease. Initially provided to the infant via breast milk, then later stimulated by gut microbiota to be produced by intestinal cells, infant fecal concentrations of secretory Immunoglobulin A (sIgA) have also been associated with later development of atopic disease when levels are low. We tested associations between breastfeeding status, infant fecal sIgA levels and C. difficile colonization.

Methods:

A subsample of 735 term infants from the Vancouver, Edmonton and Winnipeg sites of the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study were studied. sIgA levels in infant stool samples at 3-4 months were assayed using the Immundiagnostik sIgA ELISA kit. *C. difficile* levels in stool samples obtained at 3-4 months and 1 year of age were quantified by qPCR. Using SPSS v24, fecal sIgA levels of infants at 3-4 months were grouped by tertiles. Low sIgA was represented as the lowest tertile of sIgA levels. The percent of infants with low fecal sIgA levels was compared across breastfeeding status at time of stool collection (exclusive, partial, not breastfed). The association between fecal sIgA levels and *C. difficile* colonization at 3-4 months and 1 year was also determined with the Chi-square test.

Results:

Over half of infants who were not breastfed had low fecal sIgA levels compared to 38% of infants who were partially breastfed and only 10.8% of infants exclusively breastfed ($p<0.001$). At 3-4 months of age, infant fecal samples with low fecal sIgA levels were more likely to be colonized with *C. difficile* compared to those with higher sIgA levels (47.0% vs. 31.4%, $p<0.0001$). No differences in fecal *C. difficile* colonization in 1-year old infants were observed according to the amount of fecal sIgA quantified 8-9 months earlier. However, infants with low sIgA levels at age 3-4 months were also more likely than infants with higher levels to have persistent *C. difficile* colonization at 3-4 months and one year of age (23.5% vs. 15.6%, $p=0.022$).

Conclusion:

Limited breastfeeding was associated with reduced fecal sIgA levels in infants. Infants with low sIgA levels were more likely to be colonized with C. difficile colonization at 3-4 months and persistently. Hence, shorter duration of breastfeeding increases the likelihood of lower sIgA levels and C. difficile colonization, and may place infants at higher risk of atopic disease.

Funded By: Department of Pedatrics Recruitment Scholarship

Abstract #: 121
Presenter: Jack Underschultz
Supervisor: Michael Hawkes
Title: Biomarkers of pediatric pneumonia
Authors: Jack Underschultz, Ravi Barghava, Robert Opoka, Andrea Conroy, Sophie Namasopo, Jeremy Soo, Michael Hawkes
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Pneumonia is the leading cause of childhood infectious death globally. Chest x-ray (CXR) is commonly used as a diagnostic tool, but is not available in many resource-limited areas of the world where a large burden of pneumonia deaths occur. We hypothesized that serum biomarkers of inflammation, endothelial activation, and lung injury, which could be adapted to a point-of-care platform, would be associated with CXR consolidation and could be used as a diagnostic test to replace the CXR.

Methods

We conducted a cross-sectional study of 108 children under 13 years of age who were hospitalized with clinical pneumonia syndrome at two resource-limited hospitals in Uganda. Chest radiography was performed locally and interpreted by a Canadian certified (FRCPC) pediatric radiologist. Enzyme-linked immunosorbent assays were performed in order to measure the following serum host response biomarkers: C-reactive protein (CRP), Chitinase 3-like 1 (CHI3L1), Lipocalin-2 (LCN2), Tie-2, Intercellular adhesion molecule-1 (ICAM1), endoglin, Tissue Inhibitor of Metalloprotease-1 (TIMP1), and surfactant protein-D (SP-D).

Results

A total of 108 children were included (39% female) with median age 10 months (IQR 3-20 months). Based on x-ray findings, children were categorized as primary end-point pneumonia (n=24), other infiltrates (n=49), or normal chest x-ray (n=35). Clinical variables such as respiratory rate and chest indrawing were not predictive of CXR consolidation. Compared to children with normal x-ray, children with end-point pneumonia had significantly higher levels of CRP, CHI3L1, LCN2, and SP-D. CRP had the best discriminatory power (AUROC 0.73 (95%CI 0.57, 0.88) p=0.0036). Using the optimal cutoff (>35 µg/mL), CRP had a sensitivity of 71% (95%CI 53-89%) and a specificity of 79% (95%CI 65-93%) to discriminate between end-point pneumonia and normal chest x-ray. Compared to children with other infiltrates, children with end-point pneumonia had elevated CRP, CHI3L1, LCN2, ICAM1, and TIMP1. CRP had the best discriminatory power (AUROC 0.75 (95%CI 0.60, 0.89), p=0.0008). Using the optimal cutoff (>50 µg/mL), CRP had a sensitivity of 63% (95%CI 43-82%) and a specificity of 89% (95%CI 81-98%) to discriminate between end-point pneumonia and other infiltrates. Biomarkers did not differ statistically between children with other infiltrates and those with normal chest x-rays. [T1]

Conclusions

In Ugandan children with clinical pneumonia syndrome, host biomarkers distinguished between end-point pneumonia, other infiltrates, and normal chest x-ray; however, the sensitivity and specificity of any individual biomarker may not be sufficient to have clinical utility. Further work exploring the enhanced test performance characteristics of combinations of biomarkers is currently underway.

[T1]Keep the story simple

Funded By: WCHRI Summer Studentship

Abstract #: 122
Presenter: David Fung
Supervisor: Lori West
Title: Generation of allo-antigen specific thymic regulatory T cells from pediatric thymic tissue.
Authors: David Fung, Esmé Dijke, Lori West
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Tolerogenic therapy using regulatory T cells (Tregs), cells crucial for controlling immune responses, has great potential to treat autoimmunity and organ transplant rejection. Because children with autoimmune disorders and pediatric transplant recipients carry a heavy lifelong immunosuppressive burden resulting in severe morbidities from adverse drug effects, these patients would greatly benefit from this therapy. We recently showed that discarded thymus, routinely removed during pediatric cardiac surgeries, is a source of abundant highly suppressive polyclonal Tregs. Preclinical studies have shown that antigen-specific Tregs may be more effective at inducing tolerance than polyclonal Tregs. We investigated whether alloantigen-specific thymic Tregs can be generated by culturing human thymus with allogeneic monocyte-derived dendritic cells (moDCs).

Methods: Monocytes were isolated from peripheral blood of healthy adult volunteers by magnetic-bead-based cell separation of CD14+ cells and differentiated into moDCs by culturing with interleukin (IL)-4 and GM-CSF. Tregs were obtained from infant thymuses (age <1 yr) by mechanical dissociation followed by magnetic-bead-based cell separation of CD25+ thymocytes. Tregs were cultured for 7 days in the presence of moDCs with IL-2 ± rapamycin (RAPA). Suppressive function was defined by analyzing moDC-stimulated T cell proliferation with/without cultured Tregs. Phenotype and suppression were assessed by flow cytometry.

Results: Purity of the isolated CD14+ monocytes ranged from 59–86% (n=7). After differentiation, the vast majority of cells were CD14-CD86+CD11c+HLA-DR+ (n=7). After Treg-moDC culture, no Treg expansion was observed; >84% of the cultured cells were viable (n=2). For both the culture with and without rapamycin, >80% of the CD4+CD25+ cells were FOXP3+ (n=2). Suppression of proliferation was only observed in T cells stimulated with moDCs of the same donor used in the Treg culture, but not in those stimulated with third-party moDCs.

Conclusions: We successfully generated moDCs from monocytes. Although no Treg expansion was observed, the cells were viable and maintained Treg phenotype. The preliminary findings of the suppression assay suggest that alloantigen-specific Tregs were generated during culture.

Funded By: WCHRI Summer Studentship; BioCanRx Summer Studentship

Abstract #: 123
Presenter: Robert Reklow
Supervisor: Dr. Gregory Funk
Title: Importance of central equilibrative nucleoside transporters in the hypoxic ventilatory response in mice during development.
Authors: Robert Reklow, Megan Hansen, Sara Frangos, Tucaauê Alvares, Dr. Gregory Funk
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

The hypoxic ventilatory response (HVR) consists of an increase followed by a secondary depression that is modulated by purinergic gliotransmission within the preBötzinger complex (preBötC). The depression is much larger and life-threatening in premature mammals including infants. Previous results indicate that the preBötC is modulated by the balance between ATP exciation and adenosine (ADO) inhibition. Our objective was to determine the role that equilibrative nucleoside transporters (ENTs), which move ADO across cell membranes along its concentration gradient, in modulating preBötC network activity during postnatal development. We first compared the HVR of wild type (WT) and ENT 1/2 knockout (ENT KO) mice during development (P0-3 and P12-14) using whole-body plethysmography (15 min control, 10 min 10% O_2, 10 min recovery). Ventilation increases in both groups and decreases approximately 30% in WT mice during the first three minutes in hypoxia. In marked contrast, ventilation falls by 42% in ENT KO mice and, in particular, below baseline in the first 40 s in P0-3 mice. When we compared the responses of WT and ENT KO mice to microinjecting ADO (500 µM, 30 s) to preBötC in rhythmically-active medullary slices, the duration of the frequency inhibition was almost doubled in the KO mice. Additionally, bath application of the ENT-1 inhibitor (NBMPR, 100 µM) caused a significant 9.9±4% increase in baseline frequency. These *in vitro* data suggest that ENTs contribute to setting ADO_e tone in the preBötC under baseline conditions by transporting ADO into the extracellular space. However, under an extra load as might occur in hypoxia, ENTs become important in removing ADO_e. *In vivo* data are consistent with this hypothesis, but it will be critical to determine whether the differences in the HVR of WT and ENT KO mice *in vivo* reflects loss of ENT activity in the carotid bodies or central nervous system.

Funded By: WCHRI Innovation Grant; Summer Studentship; Trainee Travel Grant; CIHR; NSERC

Abstract #: 124
Presenter: Aireen Wingert
Supervisor: Lisa Hartling
Title: Adjunct Clinical Interventions That Influence Vaginal Birth After Cesarean Rates: Systematic Review
Authors: Aireen Wingert, Cydney Johnson, Robin Featherstone, Meghan Sebastianski, Lisa Hartling, R. Douglas Wilson
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Background: Rates of cesarean deliveries have been increasing, and contributes to the rising number of elective cesarean deliveries in subsequent pregnancies with associated maternal and neonatal risks. Multiple guidelines recommend that women be offered a trial of labor after a cesarean (TOLAC). The objective of the study is to systematically review the literature on adjunct clinical interventions that influence vaginal birth after cesarean (VBAC) rates.

Methods: We searched Ovid Medline, Ovid Embase, Wiley Cochrane Library, CINAHL via EBSCOhost; and Ovid PsycINFO. Additional studies were identified by searching for clinical trial records, conference proceedings and dissertations. Limits were applied for language (English and French) and year of publication (1985 to present). Two reviewers independently screened comparative studies (randomized or non-randomized controlled trials, and observational designs) according to a priori eligibility criteria: women with prior cesarean sections; any adjunct clinical intervention or exposure intended to increase the VBAC rate; any comparator; and, outcomes reporting changes in TOLAC or VBAC rates. One reviewer extracted data and a second reviewer verified for accuracy. Two reviewers independently conducted methodological quality assessments using the Mixed Methods Appraisal Tool (MMAT).

Results: Twenty-three studies of overall moderate to good methodological quality examined adjunct clinical interventions affecting TOLAC and/or VBAC rates: system-level interventions (three studies), provider-level interventions (three studies), guidelines or information for providers (seven studies), provider characteristics (four studies), and patient-level interventions (six studies). Provider-level interventions (opinion leader education, laborist, and obstetrician second opinion for cesarean sections) and provider characteristics (midwifery antenatal care, physicians on night float call schedules, and deliveries by family physicians) were associated with increased rates of VBAC. Few studies employing heterogeneous designs, sample sizes, interventions and comparators limited confidence in the effects. Studies of system-level and patient-level interventions, and guidelines/information for providers reported mixed findings.

Conclusions: Limited evidence indicates some provider-level interventions and provider characteristics may increase rates of attempted and successful TOLACs and/or VBACs, whereas other adjunct clinical interventions such as system-level interventions, patient-level interventions, and guidelines/information for healthcare providers show mixed findings.

Funded By: MNCY SCN of AHS and Alberta SPOR SUPPORT Unit KT Platform

Abstract #: 125
Presenter: Liza Bialy
Supervisor:
Title: Development of knowledge synthesis products to support health system policies and practices
Authors: Liza Bialy, Meghan Sebastianski, Robin Featherstone, Michelle Gates, Aireen Wingert, Cydney Johnson, Jennifer Pillay, Lisa Hartling
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: The Alberta Strategy for Patient-Oriented Research (SPOR) SUPPORT Unit Knowledge Translation Platform (KT platform) worked with Alberta Health Services' Maternal Newborn Child and Youth Strategic Clinical Network (MNCY-SCN) to produce multiple knowledge synthesis products to support their research priorities. These products were intended for a variety of purposes including direction for future policy changes and informing recommendations for program development and implementation. The objective of this partnership was to produce high quality knowledge synthesis products that would meet the end users' specific needs.

Methods: In collaboration with MNCY-SCN members we undertook 1 rapid response, 2 rapid reviews and 2 systematic reviews on the topics of children with medical complexities (CMC), midwifery for Indigenous populations, testing for preterm delivery in symptomatic women, and factors that influence vaginal birth after cesarean (VBAC) rates. Systematic reviews followed standard Cochrane methodology, which was adapted for the rapid reviews and rapid responses by limiting the number of databases, using a single screener and providing evidence summaries in lieu of formal data synthesis.

Results: Each of these projects resulted in a tailored methodology and knowledge synthesis product specific to the end-users' needs. For two of the topic areas (CMC and midwifery for Indigenous populations) the lead investigators were seeking a descriptive summary of the best available evidence to inform recommendations for provincial program development. The rapid review on testing for preterm delivery in symptomatic women provided evidence-based direction on accuracy and effectiveness for policy-makers, while the two VBAC systematic reviews are a first step in laying the groundwork for a quality improvement project addressing VBAC services in Alberta.

Conclusions: Knowledge synthesis products can be tailored for an end-user's specific needs to provide an appropriate level of research evidence while maintaining scientific rigour. Partnership between the MNCY-SCN and the KT platform has provided multiple avenues for the application of evidence-based knowledge in Alberta's health system.

Funded By: CIHR; Alberta Innovates; AHS Maternal Newborn Child & Youth Strategic Clinical Network; Alberta SPOR Support Unit Knowledge Translation Platform

women & children's health research institute

Abstract #: 126
Presenter: Anne Le
Supervisor: Shannon Scott
Title: Parents' experiences with pediatric chronic pain
Authors: Anne Le, Kathy Reid, Bruce Dick, Jude Spiers, Shannon D. Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Chronic pain is a significant clinical problem in pediatric populations, affecting 15-39% of children. Past research has found that pediatric chronic pain can impact not only a child's physical health but also many other aspects of life including psychological and cognitive functioning, school attendance and participation, and quality of life. Likewise, studies have indicated that parents of children with chronic pain are also highly affected by their child's condition. Despite these findings, there have been few studies looking at the experiences and narratives of parents of children with chronic pain.

Methods: 13 parents from the Stollery Children's Hospital Pediatric Chronic Pain Clinic were participated in semi-structured interviews. Data collection and analysis occurred iteratively to following-up of ideas that emerged during analysis. Qualitative descriptive approaches were used and analysis occurred in three phases: coding, categorizing, and developing themes.

Results: Analysis resulted in 3 salient themes. 1) *Parents' struggle to cope and navigate the system:* Parents described a wide range of emotions, including frustration, anger, desperation, helplessness, sadness, worry, and guilt. These feelings were largely due to the arduous process of obtaining a chronic pain diagnosis, followed by difficulties finding pain management strategies for their child. These emotions highlighted parents' struggles to make sense of what was happening and to cope with the diagnosis. 2) *Chronic pain affects the entire family*: Family life was significantly affected. Tasks, such as going out for social events or vacation became difficult to coordinate as special accommodations often had to be made, including traveling by plane instead of vehicle, scheduling frequent breaks or cancelling plans outright. Many families were affected financially, incurring costs due to having to take time off of work or paying for additional therapies. 3) *Social support is critical*: Many parents stressed the importance of a strong social support network. Family members and friends are sources of emotional support and can provide assistance with household duties while supportive coworkers and flexible hours allow parents to be able react to the unpredictable nature of the illness.

Conclusion: Pediatric chronic pain affects the entire family, especially parents. Parents experience many negative emotions while navigating the diagnosis process and potential therapies. Family life is often affected as the needs of the child with chronic pain must be taken into consideration. A strong social support network is crucial to the management of pediatric chronic pain.

Funded By: WCHRI Partnership resources

Abstract #: 127
Presenter: Hannah Brooks
Supervisor: Shannon Scott
Title: The development and usability evaluation of a whiteboard animation video for procedural pain
Authors: Hannah Brooks, Anne Le, Eleanor Fitzpatrick, Lisa Hartling, Shannon Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Emergency department (ED) procedures represent one of the most common sources of acutely painful stimuli for children. Parents often play an important role in helping their child manage their distress and pain during procedures in the ED; however, many have expressed limited knowledge in how to effectively do so. We developed a whiteboard animation video to share information with parents on how to best manage distress and pain when their child requires a needle poke.

Methods: Semi-structured interviews were conducted with parents of children seeking care in the Stollery Children's Hospital ED whose child experienced procedural pain from needle pokes. Thematic analysis was conducted, informing the development of a whiteboard animation video. Health care professionals and a Parent Advisory Group were consulted on the prototype and feedback was incorporated. The final, 3-minute, English-language video depicted a child requiring a needle poke, integrating best evidence on how parents can help mitigate their child's pain and distress.

The tool was evaluated by parents recruited from three rural ED waiting rooms in Nova Scotia, Canada. The usability survey contained 9 questions that assess the user experience of the tool. A 5-point Likert scale was used to measure their responses. Each answer was given a corresponding numerical score, with 5 being *strongly agree* and 1 being *strongly disagree*. Descriptive statistics and measures of central tendency were completed.

Results: 27 evaluated the video. Overall, parents rated the tool positively, with means of at least 3.85 out of 5.00 on all questions. When asked if parents found the tool to be useful and simple to use, most parents indicated agree or strongly agree, scoring 4.19 for both questions. Likewise, parents found the tool relevant to them as parents (4.11), the length was appropriate (4.15), the tool could be used without written or additional instructions (4.15), and that they would use the tool in the future (4.04). The highest score received was for "it will help me make decisions about my child's health", which scored 4.26. Scores for aesthetics and whether parents would recommend the tool to a friend were lower at 3.89 and 3.85, respectively.

Conclusion: Parents rated a whiteboard animation for needle poke pain management positively, suggesting this method of knowledge dissemination for pediatric conditions is highly usable. However, two aspects of the tool received slightly lower scores. We will be conducting further research and tool refinement targeting these aspects to improve the tool.

Funded By: WCHRI Partnership resources; Innovation Grant; CIHR; Alberta Innovates; Networks of Centres of Excellence of Canada

women & children's health research institute

Abstract #: 128
Presenter: Michelle Gates
Supervisor: Lisa Hartling
Title: Effectiveness of digital technologies as a distraction for acute pain in children: a systematic review and meta-analysis
Authors: Michelle Gates, Lisa Hartling, Jocelyn Shulhan-Kilroy, Tara MacGregor, Robin Featherstone, Ben Vandermeer, Naveen Poonai, Janeva Kircher, Shirley Perry, Tim Graham, Shannon D Scott, Samina Ali
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: We are undertaking a systematic review (SR) on the following question: For children (≤21 years) with an acutely painful condition or who are undergoing a painful medical procedure, what is the effect of digital technology as a distraction on their pain and distress compared to no distraction, or other forms of distraction?

Methods: In October 2017 we searched eight online databases and key grey literature sources forquantitative primary studies (any language or date); we also scanned reference lists of identified articles. Two reviewers independently screened records for eligibility and appraised study-level risk of bias, then came to consensus. Data were extracted by one reviewer and verified by another. Next steps include pooling the findings from randomized controlled trials (RCTs) via meta-analysis. We will describe the results of the remaining studies narratively. Two reviewers will independently rate the certainty in the evidence for each meta-analytic comparison for pain and distress outcomes using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: As the SR is ongoing, the following are preliminary results. We identified 2,788 unique records and included 83 studies that reported on 5,928 (median 57, range 7 to 350) children. All studies were at high risk of bias due to lack of blinding. Most of the studies were RCTs (n = 60, 72.3%) and the majority included children (2 to 11 years; n = 40/83, 48.2%) or both children and adolescents (2 to 21 years; n = 32/83, 38.6%). One study reported on a painful condition (sickle cell crisis); all others studied painful procedures, most commonly dental anesthetic injection with or without dental restoration (n = 24/83, 28.9%) and venipuncture or phlebotomy (n = 19/83, 22.9%). Common distractions were audiovisual aids (n = 34/83, 41.0%) and virtual reality (n = 20/83, 24.1%). Comparators included usual care (n = 77, 92.8%) and conventional (i.e., non-digital) distractors (n = 10, 12.0%). In approximately half (n = 44/83, 53.0%) of the studies, participants in both distraction and non-distraction groups were provided additional treatments for pain (e.g., local anesthetics).

Conclusions: We identified a large volume of research on digital technologies for distraction, especially related to AV aids and virtual reality. As a next step, we will pool data for four meta-analytic comparisons: digital technology vs. usual care; digital technology vs. conventional distractors; video games vs. virtual reality; audiovisual eyeglasses vs. projected movie. Results are expected in October 2018.

Funded By: WCHRI Innovation Grant

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Abstract #: 129
Presenter: Betty Ann Thibodeau
Supervisor:
Title: Parent's satisfaction with pediatric nurse practitioner care in a tertiary hospital
Authors: Betty Ann Thibodeau, Sarah Southon, Laura Jurasek, Wendy Beaudoin, Shirley Perry, Karen Johnston, Jolene Issel, Tamara Dorfman, Deb Olmstead
Affiliations: Other
Research Activity: Children's Health and Well-Being

Introduction: Pediatric Nurse Practitioners (PNPs) are advanced practitioners with the background skills and knowledge to deliver evidence-based, specialized health care to infants and children in a variety of settings. This unique and diverse role improves access to quality services for pediatric patients and their families. The future of Pediatric Nurse Practitioners (PNP) within the complexity of health care systems today, in part, relies on the ability of PNPs to identify the essential elements of practice that enhance parents' experience of the care provided to their infants and children. The purpose of this study was to understand parents' perceptions and satisfaction with the care provided by Pediatric Nurse Practitioners (PNPs) at a pediatric tertiary hospital.

Methods: A convenience sample of 1013 parents of children who saw a PNP were asked to complete the validated Parents' Perception of Satisfaction with Care from Pediatric Nurse Practitioners Instrument (PPSC-PNP). Parents were recruited from both inpatient and outpatient settings at the Stollery Children's Hospital in Edmonton, Canada. The confidential surveys were distributed within the practice settings of twenty PNPs working in a variety of specialty areas such as pediatric medicine, pediatric surgery, oncology and cardiology by clinic nurses, clerks or clinic staff. No parents completed more than one survey. Descriptive summaries of the data were analyzed using SPSS.

Results: A total of 537surveys were completed resulting in a return rate of 53%. Overall, 89.6% of parents were aware that their child was receiving care from a PNP. Caregivers who saw a PNP were found to be highly satisfied with the care they received (129.70/140). Clinical competency (27.77/30), communication (27.97/30) and general satisfaction (18.38/20) were rated as highly satisfied. Caregivers were most satisfied with the caring behaviors exhibited by PNP's (28.49/30). Decisional control (27.09/30) was found to be slightly lower although still in the highly satisfied category.

Conclusions: In this study parental perceptions substantiated high satisfaction with the care provided to their children by PNPs at this tertiary care hospital. Perception scores identified that parents felt their PNP's provided expert clinical care, in a uniquely caring way. This is the first study to elicit parent perceptions of the pediatric nurse practitioner role within a wide variety of specialty clinical practice settings located in a tertiary care hospital. It provides important knowledge and insight about the value of the PNP role.

Funded By: Neurosurgery Kids Fund (NSKF)

Abstract #: 130
Presenter: Sarah Elliott
Supervisor:
Title: Establishing priorities in child health: listening to and engaging with parents and families
Authors: Sarah Elliott, Shannon Scott, Antonia Stang, Amanda Newton, Joan Robinson, Lisa Hartling
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION: In child health research, the perspectives of parents are rarely acknowledged. Yet, involving them and acknowledging their needs can change priorities driving healthcare improvement. The objective of this pilot study was to engage our Pediatric Parent Advisory Group (P-PAG) in developing a priority list of research topics related to child health.

METHODS: All P-PAG members were invited to participate (n=14). A list of topics relating to child health was developed in collaboration with stakeholders and included priorities set forth by Alberta Health and Alberta Health Services' Maternal Newborn Child and Youth Strategic Clinical Network. This list was sent to parents via an anonymous online survey. The survey asked parents to rank the topics by rating the degree to which they agreed the topic was a priority. Ratings were based on a 5-point Likert scale (1-strongly disagree to 5-strongly agree). Topics that were rated 4 or 5 by ≥70% of respondents were retained for focus group discussions. Using deliberative dialogue, parents discussed and re-ranked their priority topics. All topics rated greater than 4 by ≥70% of parents made the final priority list. The McMasters Patient Engagement Evaluation tool was also used to assess how well we engaged with parents throughout the project.

RESULTS: Five active members of our P-PAG participated. Forty-six child health topics were ranked by parents. Thirteen topics were highly rated and discussed in focus groups. Eight topics were then identified as high priority and were related to: Patient Safety and Quality of Care, Trauma and Injuries, Obesity and Weight Management, Vaccines, Alcohol and Other Drug Use, Pain, Childhood Cancers, and Abuse. Two common themes were identified from narrative focus group data: "family dynamics" and "communication". In-depth discussions around these themes highlighted the need for further research into how to improve communication between patients, families, and healthcare providers. Engagement evaluations showed that we successfully and satisfactorily engaged the P-PAG in all steps from start to finish in the development (topic refinement, survey design), implementation and dissemination of this research project.

CONCLUSIONS: Utilising the knowledge and experience of our P-PAG, a list of priority topics in child health was developed. This list highlights the areas where funding and research should be directed to improve the patient care experience and child health outcomes. Moreover, themes suggest reflections that should be considered in the design, implementation and interpretation of patient-oriented research.

Funded By: WCHRI Partnership resources; Alberta Innovates

Abstract #: 131
Presenter: Samaneh Khanpour Ardestani
Supervisor: Sunita Vohra
Title: Parents and children engagement in development and validation of pediatric antibiotic-associated diarrhea measure: Rationale and design
Authors: Samaneh Khanpour Ardestani, Joan Robinson, Hien Huynh, Hsing Jou, Leo Dieleman, Sunita Vohra
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Despite their wide use, there is a disturbing lack of evidence on evaluating the validity and reliability of most commonly used pediatric diarrhea severity scales. Furthermore, most of the existing instruments are focused on acute gastroenteritis and there is no validated instrument to measure antibiotic-associated diarrhea (AAD) in children. Hence, there is a need to develop and validate the first instrument to specifically measure AAD with engaging parents and children in the development process.

Methods: A prospective longitudinal study will be conducted to validate a measurement instrument which can detect change if diarrhea occurs or improves and is able to discriminate different severities of AAD in children. *Patient engagement:* A patient advisory group including 10 parents and children will be established to identify the most important outcomes to be measured by the instrument. Their opinions will be sought to develop the items and response options, and how to access, recruit and follow up with patients to promote their participation and increase retention. Their input will also be sought for the interpretation and dissemination of the findings of the study. *Item generation:* The items of our instrument are based on i) the outcomes identified by parents and clinicians as being most important, ii) relevant constructs of a newly developed core outcome set and core outcome measurement set of pediatric acute diarrhea and iii) relevant items of two instruments of pediatric acute diarrhea: The Modified Vesikari Score and International Pediatric Acute Diarrheal Disease Scale. *Sampling frame and measurement:* After ethics approval, 120 children (birth to 17 years old) presenting to the emergency department of Stollery Children's Hospital who are newly prescribed antibiotics will be included and assessed by the instrument at the time of presentation and will be followed up daily up to two weeks after antibiotic therapy is finished. Exclusion criteria: Parental report of current diarrhea or diarrhea within the last week, children with inflammatory bowel disease or irritable bowel syndrome (chronic diarrhea), antibiotics prescribed in a low dose as prophylaxis rather than as therapy for a suspected or proven bacterial infection, and children likely to be admitted to the PICU or NICU at enrolment. *Measurement properties:* Internal consistency, inter-rater reliability, content and construct validity and responsiveness of the instrument will be examined.

Significance: With the engagement of parents and children, we will be able to design and validate the first standardized instrument to accurately measure pediatric AAD.

Funded By: Integrative Health Institute

Abstract #: 132
Presenter: Shannon Scott
Supervisor:
Title: Engaging with parents to develop innovative e-tools that merge research and story: An update on a program of research
Authors: Shannon Scott, Lisa Hartling
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: With more than 2.3 million visits annually in Canada, the emergency department (ED) care of children results in considerable financial, emotional, and resource implications for families, health systems and society. Many visits are for minor conditions that could be more aptly treated in other settings or at home (e.g., sore throats, ear infections); moreover, 1 in 5 non-admitted ED visits could be avoided. Knowledge translation (KT) initiatives that target parents and emphasize their role as a partner in health, can inform their decision-making, shape treatment expectations, and influence healthcare utilization. We have built a successful model of developing, evaluating, and disseminating effective KT tools (eBooks, whiteboards) based on the best available synthesized research and the power of the arts and story to increase parent confidence and knowledge on the most prevalent conditions for which children seek care in Canada.

Methods: Using our national parental needs assessment results (n=1097) we selected priority health conditions. Using qualitative methods, we interview parents about their experiences having a child with the conditions under study. Concomitantly we conduct systematic reviews of the best available research for management of the conditions. Working with creative writers and graphic designers, we develop composite narratives and then integrate synthesized research evidence to develop e-books, whiteboard videos and interactive infographics. Once we have a prototype, we conduct iterative feedback and refinement cycles with pediatric emergency health care professionals and parents. Refinements are made to the tools and then we conduct usability testing of each tool in ED waiting rooms across Canada. Usability testing assesses 10 aspects on a 5-point Likert scale (e.g., aesthetics, functionality, understandability). Once usability testing is completed, additional refinements are conducted and the e-tools are embedded in national platforms for pediatric healthcare (www.trekk.ca; www.echo.ualberta.ca; www.arche.ca). Targeted social media is completed to further enhance dissemination and uptake. Google analytics is regularly assessed and the research evidence underpinning each tool is re-examined every 4 months.

Findings: To date, we have developed 13 KT tools for parents focused on croup, gastroenteritis, chronic pain, procedural pain, acute otitis media and fever. We are currently developing tools for parents with a child with bronchiolitis and urinary tract infections. Our focus on developing KT tools for parents is novel and complements other initiatives that target healthcare providers.

Conclusion: The model we have developed is transferable to clinical areas beyond the pediatric ED, is scalable to international contexts, and simultaneously leverages significant economies-of-scale.

Funded By: WCHRI Innovation Grant; Partnership resources; CIHR; Alberta Innovates,

women & children's health research institute

Abstract #: 133
Presenter: Tony Ahn
Supervisor: Shannon D. Scott
Title: Developing interactive infographics as consumer-oriented knowledge translation tools for pediatric procedural pain
Authors: Tony Ahn, Anne Le, Hannah Brooks, Lisa Hartling, Shannon D. Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: ED procedures represent one of the most common sources of acutely painful stimuli for children. Though many evidence-based interventions are widely available to manage procedural pain in children, they remain severely underutilized in the emergency department (ED). In many cases, pain and anxiety induced by these procedures could be better managed. Infographics are an innovative, visually engaging medium to communicate information and hold great potential for making health research more accessible and understandable to the general public. Interactive infographics can make information sharing more engaging by introducing a sense of exploration while simultaneously having the capacity to tailor the information to the user's information needs. As a result, we developed an interactive infographic to provide evidence-based knowledge to parents about managing procedural pain.

Methods: An interactive infographic was developed based on a systematic review and a qualitative study on parent experiences and information needs relating to pediatric procedural pain. Once developed, our prototype infographic was shared for feedback with health experts and parents/families through the Translating Emergency Knowledge for Kids (TREKK) knowledge mobilization network and our team's parent advisory group. We then completed usability testing to assess parents' perceptions of the tool using a 5 point Likert scale. Usability testing was conducted in urban (Stollery Children's Hospital) and remote (Stanton Territorial Hospital) sites, and results were combined with behavioral data to refine our prototype to better meet the needs of users. Prior to dissemination, the infographic was once again evaluated for feedback from health experts and parents/families through our knowledge mobilization network and parent advisory group.

Results: Overall, our prototype was well received by health experts, parent/family advisors, and usability testing participants. All 46 parents gave favorable scores (3.74-4.49 out of 5 on all 9 survey items, though "I would use it in the future" and "It will help me make decisions about my child's health" scored relatively lower. These responses helped refine the interactive infographic, alongside user behavior data which revealed limitations of the first infographic prototype.

Conclusion: Our results suggest that interactive infographics are useful knowledge translation tools for parents and caregivers. We will continue to work alongside parents and health care professionals to create age appropriate and culturally diverse interactive infographics to provide innovative consumer-oriented interventions to enhance knowledge sharing to parents and caregivers.

Funded By: WCHRI Innovation Grant; NCE

Abstract #: 134
Presenter: Allison Gates
Supervisor:
Title: Infographics to promote trialists' awareness and uptake of the Standards for Research in Child Health: development and usability evaluation
Authors: Allison Gates, Michele Dyson
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction. In 2012, Standards for Research in (StaR) Child Health published six evidence-based Standards to guide the rigorous design and conduct of pediatric trials. While comprehensive, their format is not practical for many trialists. With the aim of promoting trialists' awareness and uptake of the Standards, we (a) identified the key messages in each Standard, (b) translated the key messages into six one-page infographics, and (c) evaluated their usability among clinicians, researchers, and trainees.

Methods. We extracted key messages from each published Standard. Next, we collaborated with a graphic design team who drafted an initial set of six infographics based on the key messages. At each stage, we sought feedback from academic colleagues and members of the Standard Development Groups to ensure the accuracy and comprehensiveness of the messages. Based on the feedback we received, graphic designers revised the infographics, creating two prototypes for evaluation. The prototypes contained identical information but differed in their design: Prototype A followed a "map-like" layout while Prototype B was linear. Over one month (April 2018), we invited members of the Maternal Infant Child and Youth Research Network (MICYRN) and the Women and Children's Health Research Institute (WCHRI) to evaluate the prototypes across eight usability domains via an online survey. We computed descriptive statistics to characterize the survey results using Microsoft Office Excel.

Results. There were 15 respondents to the survey (33% researchers, 13% clinicians/health professionals, 33% clinician-scientists, 20% students/trainees, 20% other). On a scale of 1 (strongly disagree) to 10 (strongly agree), respondents agreed that the infographics: had a clear purpose (median, range: 9, 3-10); contained relevant images and text (8, 6-10); used clear language (9, 7-10); seemed credible (9.5, 6 to 10); were preferable over detailed articles (10, 8-10); and would be helpful in designing and conducting a trial (9, 4-10). Respondents disagreed that the infographics were missing essential information (2, 1-6) and took too long to read (4.5, 2-9). Most respondents preferred the layout of Prototype A (53%) and thought that compared to Prototype B, it was more visually appealing (80%), enjoyable to read (67%), and important information was easier to find (53%).

Conclusions. In collaboration with the Standard Development Groups and graphic designers, we translated the StaR Child Health guidance into a format that appealed to the end users. Next steps will involve ongoing refinement and evaluation of the infographics and dissemination to networks of clinicians, researchers, and trainees.

Funded By: WCHRI Start-up or Retention Funding

Abstract #: 135
Presenter: Stephanie Powley Unrau
Supervisor: Shannon Scott
Title: Partnering with parents for improved pediatric health outcomes: Usability testing of a procedural pain tool in remote and urban emergency care centers
Authors: Stephanie Powley Unrau, Anne Le, Shannon Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Medical procedures in the emergency department are common, acutely painful stimuli for children within healthcare. Pain and anxiety from these procedures could be better managed. Infographics are an innovative, visually engaging strategy and understandable way to communicate health information to the general public. *Interactive* infographics communicate more information than traditional print infographics, while still being simple to use. By comparing parental response at a remote and an urban healthcare site, this study sought to determine the usability and transferability of an interactive infographic that provides evidence-based knowledge to parents about how to manage pain and anxiety when their child is undergoing a common medical procedure—needle poke.

Methods: An interactive infographic was developed based upon a systematic review and a qualitative study on parent experiences and information needs relating to procedural pain in children. Our team's parent advisory group was consulted on the development of the prototype and their key feedback was incorporated in the tested version. Usability testing was preformed in emergency departments at the Stollery Children's Hospital in a major urban center, and the Stanton Territorial Hospital in a medically remote community. The survey included 9 questions on a 5 point Likert scale for 5 evaluation elements: usability, aesthetics, length, relevance, and future use. Data between sites was compared using independent T-tests. Qualitative feedback was also collected directly after survey completion.

Results: Overall, parents gave favorable scores on all 9 survey items (mean scores ranged from 3.68-4.63/5), although "I would use it in the future" and "it will help me make decisions about my child's health" scored relatively lower. Three usability measures were rated significantly higher by parents at urban sites ($p<0.050$): "it is useful" ($p=0.044$), "it is relevant to me as a parent" ($p=0.040$), and "I would recommend it to a friend" ($p=0.000$). This was not explained by variance in demographic data between sites. New and experienced parents frequently commented that this tool is highly valuable for preparing new parents to deal with pediatric needle pokes.

Conclusions: Overall, our results suggested that interactive infographics are useful KT tools for parents in both urban and remote settings, especially for new or less experienced parents. Significant differences in our results showed that the usability, relevance, and future use of our tool varied between remote and urban sites. Further testing at remote, rural, and urban sites is needed to explain these differences and ensure representation of diverse parent perspectives.

Funded By: WCHRI Innovation Grant; Summer Studentship

Abstract #: 136
Presenter: Maria Ospina
Supervisor:
Title: Fetal hemoglobin status and its relationship to maternal hemoglobin and placental weights
Authors: Maria Ospina, Matthey Kokotilo, Andrew Woodman, Su Hwan Kim, Ferrante Gragasin, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Iron deficiency (ID) anemia is a common pregnancy complication, affecting 20-30% of pregnant women in developed countries (23% in Canada). ID anemia during pregnancy can cause adverse outcomes, including premature labour, and even fetal death. Typically, maternal hemoglobin levels are used to assess iron status in pregnancy, based on the assumption that fetal iron status mirrors that of the mother. The primary objective for this study is to evaluate the association between maternal hemoglobin (Hb) status with fetal hemoglobin status and placental weights in an obstetrical population at time of elective caesarian section.

Methods: This was aprospective cohort study of women between 18 and 50 years of age who underwent elective cesarean section for uncomplicated pregnancies at the Lois Hole Hospital for Women in Edmonton (Alberta). A Hemocue Hb 201+ system was used to assess Hb levels in mothers prior to first incision, and in mixed cord blood immediately after delivery of the newborn and after umbilical cord clamping. Backward multiple linear regression techniques were used to model maternal hemoglobin status and placental weight and their relationship to Hb status in the fetus adjusting for potential confounders.

Results: A total of 177 singleton pregnancies were included in the analysis. Mean maternal age was 32.4 years with similar delivery proportions for male (53%) and female (47%) babies. Results of the multiple linear regression showed that, after adjusting for covariates (i.e., maternal weight, birth weight, and American Society of AnesthesiologistsClass), a unit increase in maternal Hb corresponds to a significant increase in fetal Hb by 0.215 on average (95% confidence interval [CI] 0.054, 0.377). In contrast, a unit increase in placental weight corresponds to a decrease in fetal Hb by 0.0298 on average (95% CI -0.042, -0.017).

Conclusions: Both maternal Hb and placental weight were significant predictors of fetal Hb in a highly-selected population of women undergoing C-section. Results of this study should be replicated in a larger sample of women undergoing vaginal deliveries and evaluate whether both maternal Hb and placental weight are accurate surrogates of fetal anemia.

Funded By: WCHRI Start-up or Retention Funding

Abstract #: 137
Presenter: Claudia Holody
Supervisor: Hélène Lemieux
Title: Effect of perinatal iron deficiency on neonatal cardiac mitochondrial function
Authors: Claudia Holody, Andrew Woodman, Rowan Carpenter, Hélène Lemieux, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction/Objectives

Pregnant women are at risk of developing iron deficiency (ID) due to increased iron demands. Iron is essential for proper oxygen transport and mitochondrial respiration, and is therefore critical for proper fetal development. Cardiac enlargement is a critical component of the fetal adaptation to ID anemia to increase cardiac output and improve oxygen delivery to tissues. However, this process is energetically demanding, and it is unclear whether ID affects energy metabolism in cardiac tissues. We hypothesized that perinatal ID would alter cardiac mitochondrial function in neonatal rats.

Methods/Approach

Female Sprague-Dawley rats were fed either an iron-replete (35mg/kg) or an iron-restricted diet (3mg/kg before pregnancy, 10mg/kg during pregnancy). At birth, all dams were fed the iron-replete diet. At post-natal days (PD) 1, 14, and 28, hearts from male and female offspring were collected to assess mitochondrial function; electron transport system and fatty acid β-oxidation function were assessed in permeabilized cardiac fibres using High-Resolution Respirometry.

Results/Findings

Iron-deficient pups at all ages exhibited increased heart weight/body weight ratios compared to controls. Hemoglobin levels were significantly reduced in iron-deficient pups at PD 1 and 14, but not PD 28. Preliminary analysis of mitochondrial respiration shows an increased ratio of NADH pathway/Succinate pathway in ID male offspring at PD1, mainly due to a change in Succinate-pathway contribution. Experiments and analysis for other timepoints are ongoing.

Conclusions

Our results indicate a relationship between perinatal ID and sex-specific changes in mitochondrial function, at least in newborns (PD1). Mitochondrial function at all three timepoints will be compared to determine if these changes persists with age and iron repletion.

Funded By: WCHRI Innovation Grant; CIHR; Canada Foundation for Innovation, Natural Sciences and Engineering Research Council of Canada, Faculté Saint-Jean

Abstract #: 138
Presenter: Ayanna Rocke
Supervisor: Robin Clugston
Title: Maternal vitamin A status: impact on susceptibility to Congenital Diaphragmatic Hernia
Authors: Ayanna Rocke, Tim Dalmer, Tianna Clarke, Robin Clugston
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Congenital Diaphragmatic Hernia (CDH) is a birth defect that occurs in approximately 1 in every 3,000 births. It arises when the diaphragm fails to form properly during fetal development leaving a hole in the muscle. In utero, the abdominal contents protrude through the hole impeding growth of the lungs. As a result, CDH is known to cause breathing problems in newborns and is a significant cause of perinatal mortality. The cause of CDH is poorly understood. Retinoic acid is an active metabolite of dietary vitamin A, and it has been proposed that abnormal retinoic acid signaling plays a substantial role in the development of CDH. The goal of this study is to test the hypothesis that maternal Vitamin A status influences the development of teratogen-induced CDH in a mouse model. ***Methods:*** Maternal vitamin A status was manipulated by feeding mice diets with marginal, sufficient or excess-vitamin A content. Vitamin A status was confirmed in maternal tissues by HPLC. In addition, fetal tissue was collected, and vitamin A status of fetuses were determined by HPLC. We induced CDH in the offspring of mice treated with a combination of nitrofen (2,4-Dichlorophenyl 4-nitrophenyl ether) and bisdiamine (N,N'-bis (dichloroacetyl)-1,8-octamethylenediamine). Offspring were collected via dissection and the effect of the teratogen on the incidence and severity of CDH were recorded. ***Results:*** We have established a teratogenic model of CDH in mice, and determined that 0.5 g/kg of teratogen is optimal for the induction of CDH. Next, we have shown that manipulating dietary vitamin A content of female mice changes their vitamin A status, which we validated by HPLC. Fetal tissue analysis showed that resulting offspring of mice on different diets reflected the status of the mothers. Continuing studies are investigating the impact of altered maternal vitamin A status on teratogen-induced CDH. ***Conclusion:*** Teratogen treatment induces CDH in mice, and ongoing studies are examining the effect of maternal vitamin A status on this phenomenon. We expect that offspring of the mothers on a Vitamin A excess diet will have reduced incidence of CDH, while the mothers on a Vitamin A marginal diet will have an increased incidence. This research will help support the Retinoid Hypothesis and highlight the need for future studies to focus on the role of Vitamin A and its derivatives on diaphragm development.

Funded By: WCHRI Innovation Grant; Molly Towell Perinatal Research Foundation

Abstract #: 139
Presenter: Sunjidatul Islam
Supervisor: Padma Kaul
Title: Incidence of syncope during pregnancy: temporal trends and outcomes
Authors: Sunjidatul Islam, Safia Chatur, Linn Moore, Roopinder Sandhu, Robert Sheldon, Padma Kaul
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Little is known about the incidence of syncope during pregnancy. We examined temporal trends, timing, and frequency of syncope during pregnancy, and how it relates to outcomes in a large population-based cohort.

Methods: The longitudinal Alberta Pregnancy-Birth cohort consists of all live births between January 1, 2005 and December 31, 2014 in the province of Alberta, Canada. Inpatient and outpatient (clinic, emergency department, or physician office) administrative health records were used to identify women with syncope during pregnancy. Rates of preterm birth, small for gestational age (SGA), and congenital anomalies in the offspring were compared among pregnancies with and without syncope, overall, and by timing of the first syncope episode (first, second, or third trimester), and number of syncope episodes during pregnancy (1-episode and >1-episode).

Results: Of 481,930 pregnancies, 4,667 (9.7 per 1000 pregnancies, 95% confidence interval (CI): 9.4-10.0 per 1000 pregnancies) had a syncope episode. The incidence of syncope during pregnancy increased from 7.6/1,000 pregnancies in 2005 to 11/1000 pregnancies in 2014, equivalent to a 4% increase/year (rate ratio 1.04 (95% CI:1.03-1.05). Overall, 1,506 (32.3%) of the syncope episodes first occurred in the first, 2,058 (44.1%) in the second, and 1,103 (23.6%) in the third trimester; and 8% (n=377) of pregnancies had more than one episode of syncope. Compared to women without syncope, women who experienced syncope were younger (age<25 years; 34.7% vs. 20.8%; p<0.001), primi-parous (52.1% vs. 42.4%; p<0.001), and had higher rates of pre-existing medical conditions (1.8% vs. 1.0%, p<0.01). The rate of preterm birth was higher in pregnancies with syncope during the first (18.3%), compared to the second (15.8%) and third trimester (14.2%), and pregnancies without syncope (15.0%, p<0.01). SGA rates were also more common in pregnancies with syncope in the first or second trimester. The incidence of congenital anomalies among children born of pregnancies with multiple syncope episodes was significantly higher (4.7%) compared to children of pregnancies with only one syncope episode (2.4%) as well as pregnancies without syncope (2.0%).

Conclusions: The incidence of syncope during pregnancy is 1.0% and is increasing over time. Pregnancies with syncope, especially when it occurs during the first trimester, may be at a higher risk of adverse outcomes.

Funded By: A peer-reviewed research grant from the Cardiac Arrhythmia Network of Canada (CANet)

Abstract #: 140
Presenter: Esha Ganguly
Supervisor: Sandra Davidge
Title: Nanoparticle-encapsulated placental antioxidant delivery improves placental adaptation in a sex-specific manner in rat model of fetal hypoxia
Authors: Esha Ganguly, Jude Morton, Raven Kirschenman, Christy-Lynn Cooke, Patrick Case, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

Chronic fetal hypoxia associated with placental insufficiency is a common consequence of pregnancy complications such as intrauterine growth restriction (IUGR) which has been linked to fetal programming of cardiovascular disease. IUGR is associated with an under-perfused hypoxic placenta, altered placental gene expression and impaired placental function, eventually affecting development of key fetal organ systems (e.g. heart). We have previously shown that prenatal hypoxia decreased oxygenation and increased placental superoxide (O_2^-). Increased levels of O_2^- causes increased scavenging of nitric oxide (NO) to produce peroxynitrite ($ONOO^-$), thereby increasing nitrosative stress and reducing availability of NO for vasodilation. MitoQ is an antioxidant which, by encapsulation in nanoparticles (nMitoQ), can be used to reduce placental O_2^- production without crossing the placental barrier (i.e. without potential off-target effects on the fetus). We hypothesized that nMitoQ treatment prevents hypoxia-induced placental nitrosative stress and promotes placental development, ultimately leading to better pregnancy outcomes.

Methods

Pregnant rats were exposed to either hypoxia (11% O_2) or normoxia (21% O_2) from gestational day (GD) 15-21; term=22 days. On GD15, rats were intravenously injected with saline or nMitoQ. On GD21, placentae from male and female offspring were collected for detection of $ONOO^-$ (nitrotyrosine staining) and NO (DAF-FM staining). Placental labyrinth zones were collected for mRNA expression (q-PCR) of vascular endothelial growth factor (VEGF-A), a key factor in placental development.

Results

Peroxynitrite formation was increased in placentae of only hypoxic female offspring (normoxia: 0.014±0.001 a.u. vs. hypoxia: 0.018±0.001 a.u.; $p<0.05$), which was significantly reduced by nMitoQ (hypoxia-saline: 0.018±0.001 a.u. vs. hypoxia-nMitoQ: 0.015±0.001 a.u.; $p<0.05$). Placentae of prenatally hypoxic female offspring had increased NO levels (normoxia: 0.016±0.001 a.u. vs. hypoxia: 0.022±0.002 a.u.; $p<0.05$), which was not affected by nMitoQ. Prenatal hypoxia reduced VEGF-A expression in placentae from male (normoxia: 2.24±0.47 vs. hypoxia: 0.96±0.20; $p<0.05$) and female offspring (normoxia: 1.55±0.033 vs. hypoxia: 0.74±0.10; $p<0.05$) while nMitoQ increased VEGF-A expression in only placentae from hypoxic female offspring.

Conclusion

In placentae of male offspring neither prenatal hypoxia nor nMitoQ had any significant effects on NO levels and nitrosative stress ($ONOO^-$). Interestingly, both NO and nitrosative stress ($ONOO^-$) were increased in placentae of only hypoxic female offspring. nMitoQ, without changing NO levels, reduced ONOO- in placentae of only hypoxic female offspring. Additionally, nMitoQ exerted protective effects in a sexually dimorphic manner by creating a pro-angiogenic environment in only hypoxic female offspring. Treatment targeted to the placenta could contribute to improved sex-specific cardiovascular outcomes in growth restricted offspring.

Funded By: WCHRI Graduate Studentship; CIHR

Abstract #: 141
Presenter: Laura Reyes Martinez
Supervisor: Margie Davenport
Title: Sympathetic nervous system activity in women with gestational diabetes
Authors: Laura Reyes , Rshmi Khurana, Rachel Skow, Normand Boule, Craig Steinback, Margie Davenport
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Background: Gestational diabetes mellitus (GDM) affects up to 17% of the obstetric population. GDM is associated with acute and long-term cardiovascular dysfunction putting these women at higher risk of developing cardiovascular disease later in life. The mechanisms underlying these associations are not well understood. Peripheral chemoreceptors are a potent regulator of the sympathetic nervous system (SNS) and in turn, vascular function. In non-pregnant populations elevated glucose is associated with activation of the SNS and chemoreflex. However, this association has not been studied in pregnant populations. We therefore, hypothesize that women with GDM have an increased chemoreflex hyperactivity. We further hypothesize that chemoreceptor inhibition using acute high levels of oxygen may reduce SNS activity in women with GDM.

Methods: Seventeen women with GDM and 17 normoglycemic pregnant women were recruited. Muscle SNS activity (burst frequency [BF] and burst incidence [BI]) were measured using peroneal microneurography at rest, during a stress test (cold pressor test) and while the participants were breathing 100% oxygen for three minutes to assess chemoreflex.

Results: Baselinehemodynamics (blood pressure, heart rate, cardiac output, total peripheral resistance) as well as BF and BI were not different between the groups. women with GDM had an increased response in blood pressure during the cold pressor test compared to normotensive normoglycemic pregnant women (% change in MAP women with GDM 15.6 ± 1.9 % vs 7 ± 2 % in normotensive normoglycemic pregnant women; p=0.004). During the cold pressor test we found that BF and BI were similar between the groups, however, in women with GDM there is an increase in SNS activity for any increase in blood pressure (p=0.003). Women with GDM had a greater reduction of BF during hyperoxia compared to normotensive pregnant women (% change in BF in women with GDM -25.9 ± 7.4 % vs -6.5 ± 4 % in normotensive pregnant women; p=0.01).

Conclusions: Women with GDM do not display a basal increased SNS activity, however, our data suggests that their SNS activity is increased during stress. Moreover, we found thatwomen with GDM are more responsive to hyperoxia than normotensive normoglycemic controls, suggesting that chemoreflex hyperactivity can be one of the mechanisms associated with the pathophysiology of this disease.

Funded By: WCHRI Graduate Studentship; CIHR; Molly Towell Perinatal Research Foundation, Alberta Diabetes Institute

Abstract #: 142
Presenter: Stewart Rowe
Supervisor: Maria Ospina
Title: A sytematic review of the association between maternal iron status and anemia during pregnancy and iron status and anemia in neonates and infants
Authors: Jia Hang Li, Andrew Woodman, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: It has been previously shown that, among other processes, oxygen transport, immune function and physiological development all depend on the availability of iron. Despite the mirage of physiological purposes, iron deficiency (ID) remains the most common nutritional deficiency in the world, with pregnant women being especially vulnerable. While maternal hemoglobin (Hb) is regularly assessed in pregnancy, its association with fetal anemia and iron status remains unclear. Therefore, the objective of this systematic review is to evaluate the available evidence describing the association between maternal and newborn indices of iron status and/or anemia.

Methods: A comprehensive search was conducted up to May 2018 within four electronic databases. Studies were included if they were observational studies, assessed maternal hematologic profile/iron status in uncomplicated pregnancies, and included either primary or secondary outcomes. Primary outcomes were defined as hematologic or iron status indicators in newborns. Birth outcomes were considered secondary. The GATE-revised quality appraisal tool was used to assess study risk of bias.

Results: From 6,044 studies initially screened, 245 were included; 62 addressed primary outcomes, 147 addressed secondary outcomes, and 36 addressed both. Due to the large number of studies included, the current focus is on 85 English-language studies that address primary outcomes of the review. The 85 studies included 37,469 pregnant women; 41% (35) were performed in Asia, 15% (13) in Africa, 25% (21) in Europe, 11% (9) in North America, 6% (5) in South America, and 2% (2) in Oceania and Australia. A total of 26 studies assessed the correlation between maternal and newborn Hb. These correlations ranged in value from -0.06 to 0.827. Quality assessment determined that 31% (8), 27% (7), and 42% (11) had a low, moderate and high risk of bias, respectively.

Conclusion: This review will consolidate available evidence on the association between maternal and newborn ID and anemia.

Funded By: WCHRI Start-up or Retention Funding

Abstract #: 143
Presenter: Kevin Dietrich
Supervisor: Lesley Mitchell
Title: Effect of broccoli sprout consumption in late gestation on Inflammatory response gene expression, possible mechanism towards cerebral palsy reduction.
Authors: Tim Dalmer, Jerome Yager, Kevin Dietrich, Lesley Mitchell
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Intro: As 90% of developmental disabilities including cerebral palsy occur during gestation, the vulnerability of the developing brain during gestation is of great concern. Evidence has indicated that broccoli sprouts (BrSp), a source of sulforaphane, prevents detrimental neurological pathologies and behaviours through its mitigation of high oxidative and inflammatory stress on the developing fetus. One possible mechanism proposed in the rat model is that BrSp reduces the fetal inflammatory response, decreasing the severity of developmental delay.

Methods: Pregnant rats were administered injections of a saline control or lipopolysaccharide (LPS) to induce an inflammatory response on embryonic (E) day 19 and 22. Treatment groups received a supplement of dried (200 mg BrSp) starting at E14. RNA was extracted from placenta and brain tissue that was harvested either on E19 or E22. RTqPCR was then performed assessing various inflammatory response genes including IL1β precursor and active peptide, IL6, IL10, and TNFα to determine the effects of BrSp + LPS versus LPS alone in the brain and placenta.

Results: No significant differences were found when the mean fold expression change was compared between LPS and LPS + BrSp. However, it was interesting to note that LPS did not induce an inflammatory response in all pups in the examined tissues. No greater than 2-fold expression was noted in the saline + BrSp control treatment. The brain showed little response with LPS treatment.

Table 1: Summary of the percentage of pups with a greater than two-fold expression of the inflammatory response genes in the placenta. Lipopolysaccharide (LPS), broccoli sprouts (BrSp), embryonic day (E).

	IL1β		**IL6**		**IL10**		**TNFa**	
	LPS	LPS+BrSp	LPS	LPS+BrSp	LPS	LPS+BrSp	LPS	LPS+BrSp
E19	60%	60%	60%	80%	60%	80%	60%	80%
E22	40%	88%	60%	38%	40%	88%	0%	25%

Conclusions: There was an inconsistent decrease in inflammatory gene expression due to the addition of BrSp. However, a decrease in inflammatory response was indicated by the decrease in IL6 gene expression at E19. An increase in IL10 (an anti-inflammatory cytokine) expression at E22 in the placenta due to BrSp supplementation, suggests an additional role of BrSp in fighting inflammation.

Funded By: WCHRI Summer Studentship; Alberta Innovates

Abstract #: 144
Presenter: Cole Delyea
Supervisor: Shokrollah Elahi
Title: New game players: The role of CD71+ erythroid cells in feto-maternal tolerance
Authors: Cole Delyea, Najmeh Bozorgmehr, Petya Koleva, Garett Dunsmore, Shima Shahbaz, Vivian Huang, Shokrollah Elahi
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction:

The mechanism of how the female's immune system is capable of maintaining feto-maternal tolerance has puzzled immunologists for many years. Previous attempts to better understand feto- maternal tolerance involved studying the roles of multiple immune modulatory cell subsets such as regulatory T cells and NK cells. We have previously shown that newborns are physiologically enriched with CD71+ erythroid cells. These cells have distinctive immunosuppressive properties, therefore making newborns more susceptible to infection (Elahi *et al., Nature*, 2013). Additionally, we found presence of CD71+ erythroid cells in human umbilical cord blood and placenta tissues. In this study, we aimed to investigate the potential role of these cells in feto-maternal tolerance.

Methods:

We generated allogenic pregnancies by breeding BALB/C and C57BL/6 mice. Following successful pregnancy initiation, at gestational age 10.5-14.5, mice were injected with anti-CD71 antibody or isotype control, and euthanized 3 days later. The placenta and maternal spleens were collected, and immune cells were isolated for immunological studies. Pregnancy outcome was observed and isolated tissues were subjected to immunological assays.

Results:

Our data illustrated expansion of CD71+ erythroid cells in the peripheral blood, placenta, and spleen of allogenic pregnant mice. We found that depletion of CD71+ erythroid cells resulted in recruitment of pro-inflammatory cells into the placenta, and subsequently significant increases in pro-inflammatory cytokines IL-6 and TNF-α, but reduction of IL-4 and IL-10 in placental tissues. Furthermore, we found that pregnancy induced CD71+ erythroid cells express arginse-2 and PDL-1. The enzyme arginase-2 is required for their suppressive function, as supplementation of L-arginine abrogated their suppressive function *in vitro*. Finally, we observed that induction of pro-inflammatory cytokines and recruitment of immune cells into the placenta lead to fetal resorption in the absence of CD71+ erythroid cells.

Conclusion:

Our results demonstrated that CD71+ erythroid cells play an important role in regulating feto-maternal tolerance through. Our finding highlights the role of a novel subset of immunosuppressive cells in feto-maternal tolerance.

Funded By: WCHRI Summer Studentship

Abstract #: 145
Presenter: Richard Mah
Supervisor: Dr. Stephane Bourque
Title: Perinatal iron deficiency combined with a high salt diet causes sex-dependent oxidative stress and mitochondrial dysfunction in adult rat kidneys
Authors: Richard Mah, Andrew Woodman, Danae Keddie, Dr. Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Iron deficiency (ID) is the most common nutritional deficiency worldwide, for which pregnant women are most at risk due to blood volume expansion and the demands of the fetal-placental unit. Perinatal ID is associated with increased reactive oxygen species (ROS) generation and mitochondrial dysfunction in the fetal kidney, though it is unclear whether these persist into adulthood, and how an additional stressor such as a high-salt diet may exacerbate this effect. Increased ROS generation can then cause reductions in bioavailability of nitric oxide (NO), which is important for renal microcirculation and tubule function. We hypothesized perinatal ID causes sex-dependent oxidative stress and mitochondrial dysfunction in the kidney of adult offspring, which will be exacerbated by chronic high-salt intake—a known kidney stressor.

Methods: Dams were fed either an iron-replete control (37 mg/kg Fe) or iron-restricted (3-10 mg/kg Fe) diet prior to and throughout gestation. Following birth, offspring were placed on an iron-replete diet. On postnatal day (PD) 138 offspring were randomized to receive either a high-salt (HS; 5% w/w) or normal-salt (NS; 0.27% w/w) diet for 6 weeks. Tissues were collected on PD 180. Cryopreserved kidneys were sectioned and stained with markers for cytosolic and mitochondrial superoxide as well as NO with dihydrotheium (DHE), MitoSox Red, and DAF-FM Diacetate dies, respectively, and were quantified by fluorescence microscopy. Mitochondrial respiration was measured using an Oroboros -O2k Oxygraph.

Results: ID resulted in 34% and 52% decreases in maternal and offspring hemoglobin levels, respectively, compared to respective controls at birth. In 6-month old male offspring, cytosolic superoxide was increased by HS in the cortex (P=0.04), and by ID in both the medulla and cortex (P<0.001). Females exhibited decreases in cytosolic superoxide in both the cortex and medulla due to ID, albeit HS normalized levels to that of controls ($P_{interaction}$<0.05). NO production was decreased in both the cortex and medulla due to ID in males. Mitochondrial superoxide production was increased in the medulla of males subjected to HS (P=0.04), but not in females. Mitochondrial respiration was increased globally in the medulla of male offspring subjected to HS (P<0.05), albeit ID males exhibited reduced complex II derived respiration (P<0.05). Females exhibited no alterations in mitochondrial function.

Conclusion: These results suggest perinatal ID causes long-term sex-dependant patterns of oxidative stress and mitochondrial dysfunction, and males are more susceptible than females.

Funded By: WCHRI Innovation Grant; Summer Studentship; CIHR; Alberta Innovates; Canadian Foundation for Innovation

Abstract #: 146
Presenter: Camille Wiley
Supervisor: Sandra Davidge
Title: Does preeclampsia affect fetal vascular endothelial function?
Authors: Camille Wiley, Tamara Saez, Anita Quon, Floor Spaans, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Preeclampsia (PE) is a pregnancy syndrome characterized by new onset hypertension and organ dysfunction. PE is associated with poor maternal and fetal health outcomes, who have an increased risk of cardiovascular complications later in life. Although the cause(s) and mechanism(s) of PE remain unclear, one of the molecules involved in the pathogenesis of PE is lectin-like oxLDL receptor-1 (LOX-1). LOX-1 is increased in maternal vascular tissue and LOX-1 activation causes vascular dysfunction in PE. LOX-1 can also activate angiotensin II receptor-type 1 (AT1), which mediates hypertensive mechanisms in PE. This suggests a synergistic effect leading to impaired maternal vascular endothelial function. However, whether these pathways are also altered in PE fetal vessels remain unclear.

Methodology: We collected umbilical cords from the Lois Hole Hospital for Women. We assessed cross-sections for morphology and dihydroethidium (DHE) staining to evaluate superoxide radical levels. We isolated human umbilical vein endothelial cells (HUVECs) and analyzed proteins related to LOX-1 pathways by Western blotting (n=4-5). To study the effect of LOX-1-AT1 activation, we performed preliminary experiments to determine the ideal dose of LOX-1 and AT1 agonists to mimic PE conditions. We exposed HUVECs in passage 2 to 60mg/mL or 30mg/mL oxLDL, 10mM angiotensin II (AngII), or 2ng/mL TNF-a (used as a positive control for inflammatory molecules) for 8 or 16 hours (n=2). We evaluated protein expression associated with LOX-1-AT1 activation by Western blotting.

Results: No significant difference was found in superoxide radical levels between normal and PE umbilical blood vessels, however, PE umbilical veins showed a trend (Mann-Whitney test, p=0.0667) of increased oxidative stress as compared to control. Isolated HUVECs showed contamination from circulating proteins (ICAM-1 and CD31), which impaired protein analysis. In HUVECs cultures, exposure to 30mg/mL oxLDL for 16 hours appeared to increase LOX-1 expression, although 8 hours exposure to 60ug/mL oxLDL or 10uM AngII have no effect. OxLDL, AngII, and TNF-a tended to increase NOX4 expression, an enzyme that produces superoxide radicals. Exposure to oxLDL and AngII did not affect the expression of ICAM-1 (intracellular adhesion molecule-1) and eNOS (endothelial nitric oxide synthase).

Conclusions: These results suggest that LOX-1-AT1 pathways may also be involved in the pathophysiology of preeclampsia in the umbilical vein. Despite the low number of samples in this preliminary data set, additional experiments will further future aims to determine whether LOX-1 and AT1 activation mediates fetal vascular endothelial dysfunction in PE pregnancies.

Funded By: WCHRI Start-up or Retention Funding; CIHR; Alberta Innovates

Abstract #: 147
Presenter: Sauleha Farooq
Supervisor: Margie Davenport
Title: Maternal physical activity is associated with increased flow-mediated dilation during late pregnancy
Authors: Sauleha Farooq
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction:

Pregnant women are more sedentary and less active than non-pregnant populations, spending approximately 70% of waking hours sedentary. Physical activity declines with gestation reaching lowest levels in the third trimester. Flow mediated dilation (FMD) assesses endothelium-dependent vasodilation and is widely used to predict cardiovascular morbidity and mortality. Physical activity is associated with improved FMD; however, the relationships between moderate-to-vigorous physical activity (MVPA), sedentary behavior (SB) and FMD have not been explored in pregnancy. We hypothesized that late-pregnant women with higher levels of MVPA and lower SB would have an enhanced FMD response.

Methods:

FMD was measured (brachial artery Doppler ultrasonography, normalized for shear stress) in normotensive, euglycemic late pregnant women (n=46; age: 31.3 +/-3 years-old; BMI: 26.2 +/- 7.5 kg/m2) at 34 +/- 3 weeks gestation. Retrograde and anterograde velocities and flows were also calculated. Physical activity (MVPA, SB) was assessed via accelerometry for seven consecutive days (Actigraph wGT3X-BT).

Results:

Higher levels of prenatal MVPA was associated with greater FMD [min/week ($r = 0.407$; $p = 0.005$); %MVPA ($r = 0.414$; $p = 0.004$)]. However, sedentary behaviour did not demonstrate an improved FMD response.

Conclusions:

Our data suggest that increased MVPA is associated with greater endothelium-dependent vasodilation in pregnant women, which may reflect protection of maternal cardiovascular health.

Funded By: WCHRI Innovation Grant; Summer Studentship; Heart & Stroke Foundation

women & children's health research institute

Abstract #: 148
Presenter: Saba Saadat
Supervisor: Luke Eckersley
Title: The effect of doxycycline on the fetal heart-placenta axis
Authors: Saba Saadat, Denise Hemmings , Lisa K. Hornberger, Luke Eckersley
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction: Placentation and early fetal cardiovascular development may be linked. Tetracycline-inducible (Tet-On) genes can be selectively introduced into the placenta and switched on using doxycycline (doxy). However, doxy is an inhibitor of matrix metalloproteinase-1 (MMP-1) gene expression which aids in healthy placentation in pregnancy. High doses of doxy lead to dose-dependent abnormalities or fetal loss. MMPs also activate endothelin-1 (ET-1), a vasoactive peptide. Our objective is to determine the effect of doxy on the heart-placenta axis. No differences in placenta structure or ET-1 levels were hypothesized between groups when using a low dose of doxy in feed.

Methods: Mice were treated from embryonic day 6.5 with feed containing doxy (200mg/kg) (n=4 maternal mice) or control feed (n = 3 maternal mice). Analysis of fetal heart dimensions, flow, and function by M-Mode and Doppler ultrasound assessment was performed on E12.5 and E16.5. Paraffin embedded placentas were sectioned and H&E stained for analysis of placental structure/vascularity. ET-1 antibody was optimized for Western blots of a single placental lysate from each pregnancy (n=7).

Results: There was lower maternal weight gain and fewer fetuses in doxy treated dams. Placental weight was increased but fetal weight was not different. The doxy group had diastolic dysfunction. ET-1 was detected by Western blot in mouse placentas. Comparison of ET-1 expression, MMP activity and analysis of placental structure using Image J between groups is in progress.

Conclusion: There were fewer fetuses with reduced maternal weight gain after low-dose maternal doxy treatment, and fetal cardiac dysfunction. Analysis of MMP activity, ET-1 levels and placental ultrastructure and vascularity may yield further insights into these findings.

Funded By: WCHRI Seed Grant

Abstract #: 149
Presenter: Siddhi Patel
Supervisor: Georg Schmölzer
Title: Does a board game improve neonatal resuscitation skills?
Authors: Siddhi Patel, Maria Cutumisu, Caroline Fray, Matthew Brown, Thomas Jeffrey, Patrick von Hauff , Georg Schmölzer
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

More than two thirds of neonatal death are attributed to human errors during resuscitation. Therefore, the current neonatal resuscitation guidelines recommend frequent simulation based medical education (SBME). However, the current SBME approach is expensive, time-intensive, and requires a specialized lab and trained instructors. Hence, it is not offered frequently at all hospitals. However, routine SBME is important to reduce errors. We designed the board game "RETAIN" to train healthcare providers (HCPs) in neonatal resuscitation in a cost-friendly and accessible way.

We aimed to examine if a board-game based training simulator improves knowledge retention and reduces errors in HCPs.

Methods

"RETAIN" consists of a board using an image of a baby, visual objects, adjustable timer, monitors, and action cards. HCPs at Neonatal Intensive Care Unit, Royal Alexandra Hospital were invited to participate; participants had to complete a written pre-test (resuscitation of a 24-week preterm infant). Afterwards participants received instruction during a tutorial and were then allowed to do free play of newborn resuscitations. Afterwards participants had to complete a post-test (same scenario as pre-test) and an opinion survey. The intervention performed in the pre- and post-test were compared to assess knowledge retention.

Results

Thirty HCPs (four doctors, 12 nurses, and 14 respiratory therapists) participated in the study. Overall, we observed a 10% increase in knowledge retention between the pre- and post-test (49% to 59%, respectively). Temperature management showed the most knowledge gain between the pre- and post-test (14% to 46%, respectively). Mostly, placement of a hat (10% to 43%), plastic wrap (27% to 67%), and temperature probe (7% to 30%) improved between the pre- and post-test.

Conclusions

The improvement in knowledge retention warrants further clinical studies.

Funded By: Alberta Innovates -- Summer Studentship in Health

women & children's health research institute

Abstract #: 150
Presenter: Xi Chen
Supervisor: Bodil Larsen
Title: Prospective examination of micronutrient intakes in a pediatric cardiac intensive care unit
Authors: Keji Mori, Xi Chen, Vera C. Mazurak PhD, Luana Boff BSc, Cathy Sheppard RN, Lindsay M. Ryerson MD, Chloe Joynt MD, Vijay Anand MD, Bodil M.K. Larsen PhD, RDn
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction Micronutrients have essential, synergistic roles during critical illness. A high prevalence of malnutrition exists in children admitted to pediatric intensive care units (PICU) and is associated with higher risk for longer ventilator duration, hospital length of stay (LOS), risk of infection, and mortality. Micronutrient intakes have not been extensively examined in a pediatric cardiac intensive care unit (PCICU). Therefore, our objective was to evaluate micronutrient provision in a PCICU and determine its associations with hospital LOS, ventilator duration, and infection.

Methods A prospective, observational study was conducted to assess the daily micronutrient intakes of all medical and surgical pediatric (age 0-17 years) cardiac patients on nutrition support (i.e. enteral nutrition; EN, and/or parenteral nutrition; PN) admitted to the Stollery PCICU. Micronutrient intakes from all sources (EN, PN, breastmilk, additional micronutrients ordered and received) were assessed in all patients who had a minimum PCICU stay of 4 days between January 1 and March 31, 2018. Micronutrients were evaluated daily from nutrition care plans and total parenteral nutrition orders documented by a dedicated pediatric critical care registered dietitian including: vitamin A, D, E, K, C, B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12}, sodium, potassium, calcium, magnesium, phosphate, zinc, copper, chromium, selenium, manganese, iron, fluoride, molybdenum, and iodine, and compared to Health Canada's Estimated Average Requirement (EAR) or Adequate Intake (AI). Patients meeting or not meeting guidelines and infection presence was reported as proportions, with inadequate intakes compared to hospital LOS (days) and invasive ventilator duration (days), which was assessed with unadjusted logistic regression (p<0.05).

Results The median patient age was 4.6 months (2.2-9.9) with 62% male. The majority (72%) of patients had micronutrient intakes below recommendations for more than half of the micronutrients assessed. For 12 micronutrients, mean intakes fell substantially below (≤50% of the EAR or AI) recommendations, and were primarily minerals and trace elements. Positive cultures were found in 36% (n=18) of patients, and were commonly (67%, n=12) respiratory infections. In infants 30 days-6 months, a significant association was found between mean micronutrient intakes ≤50% of the EAR or AI and ventilator duration (p=0.048).

Conclusions Prospective examination of micronutrient intakes of Stollery PCICU patients suggests a high prevalence of intakes below the EAR or AI, and associations between inadequate micronutrient intakes and ventilator duration in infants 30 days-6 months. Future studies should continue to examine malnutrition and the associations between micronutrient intakes and clinical outcomes in PCICU patients.

Funded By:

The Power of Partnership

Abstract #: 151
Presenter: Manasi Rajagopal
Supervisor: William Craig
Title: An eight year review of pediatric injuries due to falls from windows and balconies
Authors: Manu Kundra, William Craig, Manasi Rajagopal, Samina Ali, Neelam Mabood, Tara Rankin, Nadia Dow
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Unintentional falls from heights such as windows and balconies pose a serious health hazard to the pediatric population. There is currently limited Canadian data describing the epidemiology of, and circumstances surrounding such falls. This study aimed to describe the incidence, demographic patterns, injury patterns and risk factors associated with pediatric falls from windows and balconies.

Methods

This study employed both retrospective medical record review and prospective data collection. Retrospectively, charts were reviewed from January 2009 to December 2014, and prospectively, consenting families were enrolled from February 2015 to February 2017. Children 0-17 years of age, who presented to the Stollery Children's Hospital Emergency Department (ED) due to a fall from a window or balcony were included.

Results

A total of 102 children were included; 72/102 (70.6%) were enrolled retrospectively and 30/102 (29.4%) prospectively. The median age was 4.46 years (IQR 2.83-6.83) with 65/102 (67.7%) being male. 89/102 (87.2%) fall cases were from windows and 13/102 (12.8%) from balconies. The mean estimated height of fall was 4.36 meters (+/- 2.50) with (59/67) 88.1% of falls occurring at the child's own home. Out of the 26 prospectively enrolled children with window falls, 25 (96.2%) had screens, 5 (21.7%) had guards, and 7 (31.82%) had stops in place. 20/23 (90%) children were noted to have climbed on furniture or other objects, leading to the fall. 31/102 (30.4%) children were admitted, out of whom 15 (48.4%) required surgery. There were no fatalities.

Conclusion

The vast majority of fall cases occurred in children under the age of 5 years and from a window. This mechanism of injury is associated with high morbidity and need for surgical treatment. Installation of key safety features in windows and balconies, and legislation to mandate this, may help minimize pediatric fall-related injuries.

Funded By: Canadian Hospitals Injury Reporting and Prevention Program (CHIRPP)

Abstract #: 152
Presenter: Avneet Mangat
Supervisor: Georg Schmolzer
Title: Magnetic non-invasive acupuncture for premature infant pain relief during routine eye-exam for retinopathy of prematurity
Authors: Avneet Mangat, Sylvia Vanos, Caroline Fray, Georg Schmolzer
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Pain is a major problem for premature infants. Premature infants undergo many painful procedures in the first weeks of life. Painful events this early in development can lead to detriments in neurodevelopment and might alter stress responses later in life. Pharmacological pain relief treatments can have negative side effects on brain structure and neurons. Therefore, it is important to develop other methods of pain relief that don't involve the use harmful drugs. Premature infants have to undergo routine eye-exam to assess for retinopathy of prematurity, which could cause blindness. This exam involves the use of a speculum that manually spreads the eyelids open, which causes pain. Our aim is to assess if magnetic acupuncture is a safe method for pain relief in premature infants who are undergoing this eye exam.

Methods

Magnetic acupuncture involves placing stickers containing magnets on specific acupuncture points. We are using stickers that are concealed with white fluid on 4 acupuncture points located on the ear. The control group has the same stickers applied at the same points but the magnets have been removed. The primary outcome is the pain response during the eye exam, which is recorded using the Premature Infant Pain Profile Score. Premature Infant Pain Profile Score is a validated and quantitative tool, to accurately assess an premature infants pain.

Results

Our project is still in progress and we will use this methodology to obtain our results.

Conclusion

Our study is on going to assess the safety, feasibility and effectiveness of magnetic acupuncture as a method of pain relief that we hope can be used universally. However, more studies should try to find any long term effects on neurodevelopment and growth with its use.

Funded By: Heart and Stroke Foundation/University of Alberta Professorship of Neonatal Resuscitation

Abstract #: 153
Presenter: Justin Lee
Supervisor: Todd Alexander
Title: Activation of the calcium sensing receptor attenuates TRPV6 mediated calcium absorption from the proximal large bowel
Authors: Justin Lee, Xiong Liu, Debbie O'Neill, Megan Beggs, Veit Flockerzi, Xing-Zhen Chen, Henrik Dimke, Todd Alexander
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

The calcium sensing receptor (CaSR) detects blood calcium (Ca^{2+}) levels and signals to either alter renal Ca^{2+} excretion and parathyroid hormone release. The CaSR is also expressed along the intestinal epithelium. However, its role in regulating intestinal Ca^{2+} absorption is unknown. Thus, we set out to examine whether the intestine contains a Ca^{2+} detecting mechanism that alters Ca^{2+} absorption in response to and therefore maintain plasma Ca^{2+}. Previous unpublished work in the Alexander lab suggested chronic CaSR activation leads to decreased the expression of transcellular Ca^{2+} absorption mediators, with the greatest effect observed on proximal large bowel. We hypothesized that the proximal large bowel comprises a Ca^{2+} sensing mechanism that appropriately alters Ca^{2+} absorption to maintain Ca^{2+} homeostasis.

Methods

To directly assess Ca^{2+} fluxes across the proximal colon, in the acute absence of calciotropic hormones, radioactive Ca^{2+} fluxes were performed *ex vivo* in Ussing chambers.

Results

Increased extracellular Ca^{2+} or basolateral application of the calcimimetic cinacalcet decreased net Ca^{2+} absorption. Conversely, Ca^{2+} absorption was increased when the extracellular buffer was switched to one containing a lower Ca^{2+} concentration. These responses were absent in mice expressing a non-functional TRPV6 (D541A). Cinacalcet also attenuated Ca^{2+} fluxes through TRPV6 in Xenopus Oocytes when co-expressed with, but not in the absence of, the CaSR. Moreover, the PLC inhibitor, U73122, prevented cinacalcet mediated inhibition of Ca^{2+} flux both in Xenopus Oocytes and murine proximal colon.

Conclusions

Together, our results reveal a regulatory pathway whereby activation of the CaSR in the basolateral membrane of the proximal large bowel attenuates Ca^{2+} absorption through a TRPV6 dependent pathway thereby maintaining plasma Ca^{2+} levels. Further studies elucidating the intestinal regulation of Ca^{2+} absorption may provide unique therapy for the diseases of Ca^{2+} imbalance and supplement poor Ca^{2+} diet.

Funded By: WCHRI Graduate Studentship; Natural Sciences and Engineering Research Council of Canada

Abstract #: 154
Presenter: Christopher Holt
Supervisor: Jackie Whittaker
Title: Sticking to it: A scoping review of exercise therapy adherence in children and adolescents (proposal).
Authors: Christopher Holt, Carly McKay, Linda Truong, Christina Le, Doug Gross, Jackie Whittaker
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Adherence to exercise therapy following musculoskeletal injury is crucial to recovery and reducing the long-term impact of these injuries. Due to physiological and environmental reasons, factors affecting adherence in youth differ from adults. The few studies examining the topic of youth exercise therapy adherence encompass a breadth of medical conditions, interventions, and outcomes. A synthesis of the existing evidence-base is needed to consolidate what is known about youth exercise therapy adherence to inform exercise therapy program implementation. The *primary objective* of this review is to consolidate facilitators and barriers of youth exercise therapy adherence across medical conditions. *Secondary objectives* include summarizing the relationship between adherence and clinical outcomes, and identifying interventions known to improve adherence to youth exercise therapy.

Methods: TheArksey and O'Malley framework, revised by Levac, was used to structure this scoping review. Six electronic databases were searched using a strategy (keywords and medical sub-headings), developed with a medical librarian-scientist, for records that include: English language, original data (including grey literature), exercise therapy intervention, outcome or construct of adherence, and youth (age 0-18 years) samples. All raters have had inter-rater reliability tested through screening a random sample of titles/abstracts (blinded to author and journal title) and comparing results with senior author (≥85% agreement required). Two raters will independently complete title and abstract screening, followed by full manuscript review and methodological quality assessment using the Downs and Black checklist. Final search results will be presented in a PRISMA style diagram. Data collection will evolve based on records retrieved. Extracted data will be summarized using original quantitative and thematic analyses.

Results: 4,939 records were identified by the search strategy, with approximately 50 – 75 records expected to meet criteria for inclusion in the review. Extracted data will include sample characteristics (e.g., age, sex, medical condition), adherence outcomes, adherence estimates, adherence measurement tools, reported barriers and facilitators of adherence, interventions hypothesized to impact adherence, and clinical outcomes.

Conclusions: This scoping review will explore the multiple components of adherence to exercise therapy in youth across a variety of conditions. This knowledge will be consolidated and re-applied in an innovative way to significantly help inform future research into youth exercise therapy program implementation. Ultimately, improving youth exercise therapy adherence will be critical to helping front-line clinicians improve outcomes and decrease both the cost and impact of musculoskeletal injury for our active youth.

Funded By: WCHRI Graduate Studentship; CIHR

Abstract #: 155
Presenter: Lesley Brennan
Supervisor: Irena Buka
Title: Pediatric exposures to cannabis: Cases presenting to the children's environmental health clinic (ChEHC)
Authors: Lesley Brennan, Anne Hicks, Alvaro Osornio-Vargas, Alexander Doroshenko, Donald Spady, Irena Buka
Affiliations: Other
Research Activity: Children's Health and Well-Being

Introduction

In October 2018, personal use of cannabis will become legal across Canada, permitting adults 18 and older to buy and use cannabis from a provincially-licensed retailer, and grow up to 4 plants for personal use in their home.

Children are a uniquely vulnerable population. They display exploratory behaviors, proportionately breathe in more air (and therefore pollutants as well), and have a higher metabolic rate and a fluid state of neurocognitive development. With Canada transitioning to legal cannabis use there is concern that children are at risk for unintentional exposure to cannabis through passive smoke inhalation or accidental ingestion. Understanding the impact of unintentional cannabis exposure on the health and wellbeing of children is in its infancy. Children have no power over the decisions made in their homes, therefore it is critical that Canadians have the information they need to protect their children.

The Children's Environmental Health Clinic (ChEHC) addresses the impacts of environmental exposures on Children's Health. In the years leading up to legalization, ChEHC has cared for several children exposed to cannabis. The objective of this case series is to describe susceptible children and potential health effects, setting the stage for future research.

Methods

The ChEHC patient database from 2012-2015 was reviewed for patients with cannabis exposure identified by the referring provider or though intake screening. For each patient, age, demographics, home characteristics, exposure circumstance, health status, and outcome were recorded.

Results

Six cannabis exposure cases presented to ChEHC between 2012-2015. Most children were under age 5. Three homes were legal grow-operations. Adults smoking cannabis in proximity to children was frequently noted. In one case, cannabis smoke was from a neighboring rental unit. Another involved a teenager experimenting with cannabis. The identified health effects in these children were primarily respiratory; one also noted difficulty concentrating. One case of regular cannabis use in pregnancy was also noted.

Conclusions

This case series indicate that children in cannabis-using environments may be exposed, with health consequences. As cannabis becomes more accessible in Canadian homes, the incidence, prevalence and type of pediatric exposures and resultant health effects need to be evaluated. Cases of exposure from neighbors in multi-dwelling units may help inform legislation. Exposure during pregnancy and breastfeeding is another area that requires more research. Research and communication among health professionals and families will be critical in the legalization era.

Funded By: Covenant Health Research Centre

Abstract #: 156
Presenter: Nicholas Kuzik
Supervisor: Valerie Carson
Title: A descriptive study of physical activity and parent-child proximity in early years children
Authors: Nicholas Kuzik, Valerie Carson
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Objective: The objective of this study was to describe early years children's (18-60 months) physical activity and concurrent parent-child proximity.

Methods: Fifty-four parents and children wore ActiGraph wGT3X-BT accelerometers on their waists 24 hours/day for seven days. Parental accelerometers continuously emitted Bluetooth signals, while children's accelerometers recorded one signal/minute. Accelerometer data was downloaded in 15-seconds epochs for parents and children. Light-intensity physical activity [LPA] (Child: 26-419, Parent: 25-504 counts/15sec) and moderate- to vigorous-intensity physical activity [MVPA] (Child: ≥420, Parent: ≥505 counts/15sec) were classified by accelerometer data. Based on a previous validation study, children's physical activity was grouped by detection of Bluetooth signals (i.e., no proximity [NP] or proximity). When proximity was detected children's physical activity was further grouped by parent-child co-activity [Co] or parent close but mismatching behaviours [Close]). All data analysis was completed in R (version 3.4.0).

Results: The average number of valid days for children and parents was 6.20 ± 1.39. Children accumulated 4.84 ± 0.52 hours/day of LPA, of which 51.05% was NP-LPA, 27.00% was Close-LPA, and 21.96% was Co-LPA. Children accumulated 1.34 ± 0.33 hours of MVPA/day, of which 51.11% was NP-MVPA, 23.89% was Close-MVPA, and 25.30% was Co-MVPA.

Conclusions: Children accumulated just over half of their physical activity outside of parental proximity according to Bluetooth signals. Distributions of proximity were similar between LPA and MVPA. Future research will build on this preliminary data by increasing the sample size to examine the associations between parent-child proximity and physical activity, stationary time, and sleep.

Funded By: WCHRI Graduate Studentship

Abstract #: 157
Presenter: Sonya Widen
Supervisor: Andrew Waskiewicz
Title: bmp3 is a novel regulator of neural crest cells and ocular fissure closure
Authors: Sonya A. Widen, Lisa B. Prichard, Ordan J. Lehmann, Andrew J. Waskiewicz
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Ocular coloboma is a congenital, frequently blinding condition that results from failure of the optic fissure to close. Along with etiologically related diseases, coloboma represents up to 11% of all pediatric blindness. While there are many genetic lesions that are known to cause coloboma, they represent a fraction of all documented cases; therefore, our goal is to elucidate novel genetic causes of coloboma. Recent work on Transforming Growth Factor β (TGF-β) signaling has demonstrated its role in ocular fissure closure through ECM breakdown during fusion. Here, we describe an intriguing new candidate in causality of coloboma, *Bone Morphogenetic Protein-3* (*BMP3*), a TGF-β ligand.

Methods

To identify genetic variants in patients with coloboma, we performed Sanger and exome sequencing. We employed morpholino (MO)-based knockdown and CRISPR-Cas9 mutagenesis to investigate roles of *bmp3* in ocular development, in situ hybridization (ISH) for gene expression analysis, pSmad3 immunohistochemistry (IHC) to visualize TGF-β signaling, and transgenic zebrafish for fluorescence microscopy and cell migration analysis. We utilized western blots, *in silico* ANOLEA, and online prediction tools to investigate the pathogenicity of identified mutations.

Results

Exome sequencing of affected individuals in a pedigree identified a novel variant in *BMP3*; two additional variants within the functional domain were identified through Sanger sequencing of a coloboma panel. *In silico* modeling, Polyphen and MutationTaster indicate variants are damaging to protein function, whilewestern blots suggest one BMP3 variant has altered protein secretion. In zebrafish, ISH shows *bmp3* is expressed specifically in head mesenchyme directly anterior and ventral to the developing eye. We show that TGF-β signaling is active within the ventral-nasal lobe of the retina, directly adjacent to cells expressing *bmp3*. Ventral retinal gene expression is altered in *bmp3* mutant embryos and fissure closure is delayed compared to controls; this suggests a possible link between Bmp3 and fissure closure. Additionally, *bmp3* morphants display fewer periocular mesenchyme (POM) cells, a subpopulation of neural crest required to mediate fusion between the two fissure margins, representing a second possible mechanism for Bmp3 in ocular fissure closure. Current work focuses on further characterizing mutant phenotypes to elucidate the molecular mechanism of Bmp3 in fissure closure and causality of ocular coloboma.

Conclusions

We have identified sequence variants in a novel candidate in causality of ocular coloboma, *BMP3*. Zebrafish experiments suggest Bmp3 is activating TGF-β signaling in the ventral-nasal retina where it may regulate retinal gene expression and POM to ensure successful ocular fissure closure.

Funded By: WCHRI Innovation Grant; Graduate Studentship; Trainee Travel Grant; CIHR, Alberta Innovates, NSERC

Abstract #: 158
Presenter: Andrew Chan
Supervisor: Edmond Lou
Title: Image registration of CT and 3D ultrasound (3DUS) vertebral surfaces for adolescent idiopathic Scoliosis surgery
Authors: Andrew Chan, Eric Parent, Edmond Lou
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Adolescent idiopathic scoliosis surgery is commonly indicated for severe scoliosis to correct deformity and restore spinal balance. During surgery pedicle screws are inserted into narrow thoracic pedicles, risking neurologic injury. Using image guidance to aid screw placement may reduce risk of pedicle breach but increases exposure to ionizing radiation. A potential replacement to guide screw placement may include 3D Ultrasound (3DUS). Ultrasound-imaged vertebral surfaces can be reconstructed into 3D and then registered to pre-operative 3D spinal imaging to provide visual feedback on optimal screw insertion trajectory. This study aims to determine the accuracy and speed of an image registration program for CT and 3DUS vertebral surfaces.

Methods: Optitrack Prime 13W cameras with 0.25mm and 3° accuracy were combined with an Ultrasonix SonixTablet with 6.67MHz, 38mm linear transducer with 0.2mm accuracy to create 3D reconstructions of vertebral surfaces. The CT scan of a phantom T6 vertebra was segmented, 3D printed and imaged in a water bath with the 3DUS. Registration software was developed to translate and rotate CT scans to be registered to the 3DUS vertebral surface scan. Mean squared error between the two image volumes was calculated to optimize registration quality. The vertebral surface was registered 28 times, each with the ultrasound surface rotated in two directions by up to 45°. Each registration was timed and accuracy was evaluated by manually transforming volumes to determine if a more optimal registration could be achieved. Registrations within 1minute and requiring less than 2mm and 5° transformation were considered successful.

Results: Automated registration of the T6 vertebra required 19.9±1.28s on a Core i7 3.6 GHz Processor with 16GB RAM. Of 30 registrations, 24 were successful with accuracies of 0.51±0.41mm and 2.8±1.8° based on manual transformation. The six failures involved vertebrae tilted in two directions greater than 35° with errors of 3.4±1.2 mm and 12.9±4.1° While vertebrae are unlikely to oriented at these extreme angles in surgery, additional iterations of rigid transformations to cover a wider range of positions and orientations could help to improve software robustness. Additional vertebral levels also need to be tested to ensure the system is useable for the entire spine.

Conclusions: Image registration of individual vertebrae 3D ultrasound images with CT scans are able to achieve adequate registration accuracy while requiring a reasonable amount of time to use in the operating room, though further investigation is needed to cover a wider range of angles and vertebrae.

Funded By: WCHRI Trainee Travel Grant; Alberta Innovates; NSERC

Abstract #: 159
Presenter: Linda Truong
Supervisor: Jackie Whittaker
Title: Identifying the non-physical rehabilitation needs of youth after a musculoskeletal injury: A scoping review
Authors: Linda K. Truong, Amber D. Mosewich, Chris J. Holt, Christina Y. Le, Maxi Miciak, Jackie L. Whittaker
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION

Sport participation has numerous benefits including the promotion of physical and mental health while improving quality of life. In Canada, it is estimated that two out of three injuries that occur annually in youth are linked to sport. For decades, the primary focus of sport injury rehabilitation has emphasized managing physical needs despite growing evidence that non-physical (e.g. psychological, social, contextual) needs play an important role in recovery. Therefore, holistic rehabilitation programs addressing both physical and non-physical needs are vital to ensuring that youth who suffer a sport-related injury experience a safe and successful return to sport and recreation. Currently, the evidence related to non-physical rehabilitation needs is dispersed across a broad spectrum of sport-related musculoskeletal injuries and disciplines. The primary objective of this review is to identify the non-physical rehabilitation needs of youth aiming to return to sport or recreation after a musculoskeletal injury. Secondary objectives include summarizing the methods to clinically assess and manage these needs.

METHODS

This comprehensive scoping review followed Arksey & O'Malley's 5-stage framework. Six databases (MEDLINE, PsycINFO, CINAHL, SportsDiscus, Scopus, ProQuest) were searched using predetermined search terms developed in conjunction with a librarian scientist. Selected studies included; English language, original data, youth (11-18 years of age) with a traumatic time loss sport or recreation musculoskeletal injury, and discernible non-physical (psychological, social, contextual) rehabilitation needs. Two authors were involved at each stage and independently reviewed titles and abstracts, and full text articles including quality assessment (Mixed Methods Appraisal Tool). Extracted data will be summarized using descriptive and thematic analyses.

RESULTS

Of 7276 potential records, 4733 unique records were identified. Prior to title and abstract review, we assessed the applicability of exclusion criteria and inter-rater agreement (Cohen Kappa Coefficient >0.80) with 120 records. 280 records were identified for full-text review with 80 studies meeting the inclusion criteria. Data extraction including study and sample characteristics (i.e. age, sex, injury type, sport type), non-physical needs (categorized by domains and rehabilitation stage), and quality assessment is currently underway. If applicable, methods for assessing and managing specific non-physical rehabilitation needs will be extracted.

CONCLUSIONS

This review will provide a much-needed summary of the non-physical rehabilitation needs of youth that suffer a sport-related musculoskeletal injury. This information will provide a foundation for understanding the impact of non-physical rehabilitation needs on recovery and inform future studies aimed at developing holistic evidence-based rehabilitation strategies after a youth sport-related injury.

Funded By: Faculty of Rehabilitation Medicine

Abstract #: 160
Presenter: Paul Chrystal
Supervisor: Ordan Lehmann
Title: Loss of the transcription factors foxc1a and foxc1b recapitulates ARS phenotypes and suggest a novel role in left-right patterning
Authors: Paul Chrystal, Curtis French, Ann-Marie Peturson, Andrew Waskiewicz
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Axenfeld-Rieger Syndrome (ARS) is a rare genetic disease first described in 1920 that arises due to mutations in the transcription factors *FOXC1* and *PITX2*. Our understanding of the disease etiology remains incomplete due to the complex nature of this multi-system disorder; children with ARS may present with early-onset glaucoma, ocular anterior segment dysgenesis, dental and craniofacial dysmorphism, hydrocephalus and/or cardiac valve and septal defects. Although *PITX2* has long been established as a downstream target of *NODAL* (a patterning gene of left-sided identity for the heart), no evidence has linked *FOXC1* to the left-right axis. In this study we generated a new zebrafish model of ARS, demonstrated that it recapitulates many of the human features, and propose a novel mechanism for ARS-associate congenital heart defects.

Methods/Approach

CRISPR/Cas9 genome editing produced a 7bp and 40bp deletion upstream of the DNA-binding domain of the zebrafish paralogs *foxc1a* and *foxc1b* respectively. Gross developmental defects were identified via live brightfield microscopy over the first five days of development. In situ hybridisation was utilised to investigate organ situs and left-right patterning of the organ precursors. Examination of cilia length in the left-right organiser (LRO) was performed by wholemount immunofluorescent imaging against acetylated tubulin. Full-length *foxc1a* and *foxc1b* RNA was injected into a one-cell stage embryo for ubiquitous gene overexpression studies.

Results/Findings

Compound *foxc1a*$^{-/-}$; *foxc1b*$^{-/-}$ homozygotes had almost complete penetrance of pericardial oedema (25/28) and >65% penetrance of craniofacial dysmorphism (19/28) and hydrocephalus (21/28). Closer examination of the heart revealed profound cardiac situs disturbance with only 38% of embryos forming normal D-looped hearts and a majority failing to move from the midline. Disturbance of left-sided *spaw* expression (*NODAL* ortholog) was observed in 30% of *foxc1a*$^{-/-}$; *foxc1b*$^{-/-}$ suggesting a partially penetrant left-right patterning defect of the lateral plate mesoderm upstream of *pitx2*. Immunofluorescence revealed a trend towards shorter axonemal length with loss of *foxc1a/b* and increased axonemal length with overexpression of *foxc1a/b* paralogs in LRO cilia. Such changes have been shown to impact nodal flow and *spaw* asymmetric expression previously, although other mechanisms have not yet been discounted.

Conclusion

Here we demonstrate that compound *foxc1a*$^{-/-}$; *foxc1b*$^{-/-}$ homozygotes recapitulate several of the characteristic phenotypes of Axenfeld-Rieger Syndrome including hydrocephalus, craniofacial dysmorphism and disturbed cardiac development. These data are the first to suggest a link between the transcription factor *FOXC1* and cardiac situs determination and may therefore implicate subtle left-right patterning changes with the congenital heart defects observed in ARS patients.

Funded By: CIHR

Abstract #: 161
Presenter: Jesse Orjasaeter
Supervisor: David Nicholas
Title: Approaches perceived to promote allyship between researchers and the ASD community
Authors: Jesse Orjasaeter
Affiliations: Other
Research Activity: Children's Health and Well-Being

Introduction/Objectives: This research aims to explore and promote 'allyship' and collaboration between researchers and the autism spectrum disorder (ASD) self-advocate community in: (i) identifying key approaches for building allyship, (ii) seeking meaningful opportunity for the engagement of autistic adults in partnership with researchers, (iii) advancing relationships between autistic adults and others within the research community in terms of research partnership, and (iv) identifying potential goals and foundational elements in the development of allyship between autistic people and the research community. **Methods/Approach:** In addressing the lack of meaningful community involvement in research, and towards moving current relationships forward between the ASD and non-ASD community, this research asks the question: 'what are perceived best approaches to promoting allyship between researchers and the ASD community?' This study will utilize two mixed focus groups, with thematic analysis taking place after each round of data collection. Each focus group will be formed of autistic self-advocates and academic researchers in the area of ASD. In addition, there is the potential for a wider intersectional discussion to develop, regarding the common challenges to allyship faced by disparate populations (e.g., Indigenous communities, LGBTQ2S+ communities) and by examining how collaboration has been approached in these populations. Methodologic decisions will be made according to principles of community-based participatory research (CBPR), and guided by a critical theoretical framework and overall interpretive description approach. **Results/Findings:** A preliminary literature review has been conducted which provides an outline for previous work that has demonstrated potentially collaborative research engagement between autistic people and researchers. Some approaches identified are CBPR, community academic partnership (CAP), participatory action research (PAR) and emancipatory research. This review demonstrates a gradual shift over time from more positivist research designs where the academic is lead researcher, to recent emancipatory research led by autistic self-advocates and work such as by Academic Autistic Spectrum Partnership in Research and Education (AASPIRE). Despite an increase in research utilizing collaborative and partnership-based approaches, there is a wide range of definitions relative to what is considered 'genuine' research engagement. **Conclusion:** This research is seeking to engage in meaningful and authentic connection with autistic people as expert and valued commenters of research about them. By sharing identified approaches that encourage increasingly relational and allied values in research, autism self-advocates can more fully participate, engage in, and lead research regarding their own lived experiences, thus generalizing these values of authentic inclusion, partnership and ultimately greater participation in society at large.

Funded By: Autism Edmonton, and Autism Research Centre (Glenrose Hospital)

women & children's health research institute

Abstract #: 162
Presenter: Keji Mori
Supervisor: Jackie L. Whittaker PT, PhD
Title: Dietary intake in youth with a sport-related knee injury: Implications for secondary prevention of osteoarthritis
Authors: Keji Mori, Xi Chen, Vera C. Mazurak PhD, Luana Boff BSc, Cathy Sheppard RN, Lindsay M. Ryerson MD, Chloe Joynt MD, Vijay Anand MD, Bodil M.K. Larsen PhD, RD
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction Sport and recreation participation is the leading cause of injury requiring medical attention amongst Canadian youth, with approximately 40% of injuries affecting the knee. Knee injuries increase the risk for osteoarthritis (OA), with 50% of youth who suffer significant knee injuries developing OA within 10-15 years. As OA has no cure, preventative strategies are needed. Diets meeting nutritional guidelines may serve as a possible preventive treatment modality following joint injury due to the role of key nutrients in bone and joint health. This study describes the dietary intakes of youth with and without a recent sport-related knee injury in comparison to Dietary Reference Intakes (DRIs).

Methods Participants included 37 youth who suffered a sport-related knee injury within the last 3-months, and 14 uninjured controls. Dietary assessment consisted of a self-reported 3-day food record, logged through a web-based application (MyFitnessPal©). Dietary records were analyzed using FoodProcessorII©. Intake of macronutrients (protein, carbohydrates, fat, fiber), and selected micronutrients (omega-3, vitamin A, D, E, K, C, calcium) important for bone and joint health were compared to DRIs (including the Acceptable Macronutrient Distribution Range, Estimated Average Requirement; EAR, and Adequate Intake; AI) as appropriate. Descriptive statistics [median (range) or proportion] were calculated for all participant characteristics, and the proportion of participants not meeting, or substantially below (≤50% of the EAR or AI) requirements, were reported. Finally, unadjusted logistic regression was used to explore between group differences in the proportion not meeting DRIs (p<0.05).

Results The median participant age was 17 years (range 15-19) and 71% were female. The majority of participants met protein and carbohydrate DRIs with 51% exceeding fat DRIs. Amongst both study groups, there was a high prevalence of participants not meeting guidelines for fiber (86%), vitamin D (100%), E (86%), K (63%), and calcium (69%). Intake of vitamin D was substantially below (i.e. ≤50% of the EAR) guidelines for 67% (n=34) of participants. Injured participants were observed to be more likely to not meet omega-3 guidelines, compared to uninjured participants (OR 0.23; CI: 0.6,0.86; p=0.03).

Conclusions Preliminary findings investigating the diets of youth with and without a knee injury suggest many are not meeting dietary guidelines for nutrients vital to bone and joint health, including fiber, vitamin D, E, K, and calcium. The diets of sport-injured youth warrant further investigation, as a secondary preventative approach to support optimal knee recovery and mitigate risk for early OA.

Funded By: Arthritis Society, Faculty of Rehabilitation Medicine; University of Alberta, Undergraduate Research Initiative

Abstract #: 163
Presenter: Aiza Khan
Supervisor: Consolato Sergi
Title: Sialidosis:A review of morphology and molecular biology of a rare pediatric disorder
Authors: Aiza Khan, Consolato Sergi
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Sialidosis (MIM 256550) a lysosomal storage disease caused by mutations in the NEU1 gene, resulting in α-N-acetyl neuraminidase deficiency. The subsequent deficient enzyme activity causes impaired processing/degradation of sialoglycoproteins, leading to intracellular accumulation and urinary excretion of the sialyl oligosaccharide. Complete understanding of the molecular pathways of underlying pathogenesis of this rare disease remains difficult. Therefore limiting therapeutic options. This study is an attempt to combine and review the underlying molecular biology, the clinical and morphological features of sialidosis.

Methods: Firstly a thorough electronic search on Google Scholar, Scopus, and PUBMED, during the period from January 1980 to January 2018. The words used in the search included sialidosis I, sialidosis II, congenital sialidosis, infantile sialidosis, juvenile sialidosis, and combinations. Sialidosis I is discussed briefly in this study as it appears later in life. However, all found cases of sialidosis II were included since this condition presents in the pediatric group of patients.

Results/Discussion: Till date, 40 mutations of NEU1 have been reported. There is a molecular heterogeneity, and a variety of clinical phenotypes present either as sialidosis I or sialidosis II, with fluctuating levels of severity. Sialidosis, an autosomal recessive disease, has been divided into two subtypes, based on clinical symptoms, ages of onset. Sialidosis type I (normomorphic) and sialidosis type II (dysmorphic). Sialidosis II is subdivided into (i) congenital; (ii) infantile and (iii) juvenile. Researchers have also suggested to divided NEU1 protein variants into three groups, which helps in understanding the different types of sialidosis. According to which, in the first group, the mutant enzyme is catalytically inactive and also does not localize to the lysosomes (causing congenital, severe type of sialidosis II) whereas, in the second group, the mutant enzyme localizes to the lysosomes, but stays enzymatically inactive (Infantile/Juvenile type of sialidosis II). In the third group, the mutant protein has residual activity and also localizes to the lysosomes, leading to Sialidosis I.

Conclusion: Currently there is no effective therapeutic option for sialidosis. In sialidosis I, the myoclonus can be debilitating, but other symptoms are relatively mild and appear late. Researchers have emphasized that establishing therapeutic intervention for sialidosis I should be prioritized to improve the quality of life. While in sialidosis type II, patients exhibit a fulminant course, hence creating an effective treatment for type Sialidosis II remains difficult. For now Carrier detection, prenatal molecular diagnosis, and improved genetic counseling is a satisfactory strategy.

Abstract #: 164
Presenter: Joanne Lemieux
Supervisor:
Title: Understanding the role of rhomboid protease GlpG in pathogenic bacterial colonization
Authors: Joanne Lemieux, Tiffany Lo, Elena Arutyunova, Heather Armstrong, Eytan Wine
Affiliations:
Research Activity: Children's Health and Well-Being

INTRODUCTION: The rhomboid protease gene *glpG*was recently shown to be essential for Extra-intestinal Pathogenic *E. coli* (ExPEC) colonization in the mouse gut[1].ExPEC colonization occurs naturally in the gut, however these strains can spread to other niches leading to pathologies: blood infections and urinary tract infections (UTI). UTIs occur disproportionately in women. Furthermore UTIs in pregnant women can lead to vertical transmission to neonates, which can cause sepsis and morbidity.

Rhomboid proteases are membrane-embedded serine proteases that cleave and release signalling molecules from membranes[2]. Theyare ubiquitously expressed and linked to several major disease states including cancer and neurodegenerative disease. The *E. coli*rhomboid protease, GlpG, is essential for colonization extra-intestinal pathogenic *E. coli*, bacteria responsible for urinary tract and neonatal infections[1,3].Despite the accumulated knowledge on rhomboid proteases, many questions remain unanswered for this important class of enzymes, in particular for the role of GlpG in ExPEC colonization.

METHODS: This research project focuses on whether a correlation exists between bacterial strains' pathogenicity and their *glpG* mRNAand GlpG protein levels. Biochemical methods including RT-qPCR, Western blot analysis and growth curves will be used.

RESULTS:Using RT-qPCR, glpG mRNA levels in different pathogenic, probiotic, commensal, as well as pathobiont strains were evaluated. Higher *glpG*mRNA levels were observed in pathogenic and pathobiont strains compared to the laboratory K12 wild type strain. To monitor the phenotypic differences between bacterial strains, growth condition studies for K12 wild type and K12-*glpG*knock-out strains were conducted by generating growth curve in M9-glucose media and M9-mucin media. Growth condition study revealed a slight growth deficiency in K12-*glpG*knock-out strain in comparison to the K12-wild type strain, an indication that GlpG may play a metabolic role in *E. coli*. This growth study will be extended to include pathogenic, probiotic, and pathobiont strain.

CONCLUSIONS: Preliminary analysis indicates pathogenic *E. coli*strains have higher GlpG transcript levels compared to non-pathogenic strains, and knockout results in growth defects under minimal media conditions. A reporter assay is being developed to evaluate GlpG protein expression levels in the bacterial strains. This work provides an essential framework to bridge the gap in our understanding of rhomboid protease function at the molecular level to determine its role in bacterial colonization, towards the goal of developing therapeutics to treat EXPEC infections in women and children.

Funded By: WCHRI Innovation Grant

Abstract #: 165
Presenter: Amanda Liu
Supervisor: Diana Mager
Title: Health Professional and Community Perceptions Regarding Content Development for a Gluten Free Diet Nutrition Guide
Authors: Amanda Liu, Peggy Marcon, Justine Turner, Kristin Harms, Diana Mager
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Celiac Disease is a common childhood autoimmune gastrointestinal disorder, treated with strict adherence on the Gluten Free diet. This diet is known to be high in simple sugars and saturated fat, and low in important micronutrients leading to an increased risk for suboptimal nutrient intake and impaired development. Current nutritional guidelines are not tailored for such specific dietary restrictions and thus do not address the nutritional deficiencies. A specialized food guide is needed to help families make healthy gluten-free food choices.

Objective: The objective of this study is to probe stakeholders (health professionals, Celiac patients and their caregivers) to develop content for a Gluten-Free nutrition guide.

Methods: Two internet surveys (health professional and community members) were circulated through the Canadian Celiac Association and health professional associations. Survey content addressed demographics (location, type of professional practice, length of Celiac diagnosis) and perceptions on food guide content (nutrition topics, menu planning, label reading, etc...). Descriptive statistics were used to analyze closed-ended questions and thematic analysis for open-ended questions.

Results: 249 health professionals and 409 families responded. Health professional respondents consisted mainly of registered dietitians (80%) who saw a Celiac case 1-5 times per month (82%). Family respondents were caregivers, 31-40 years old (34%) with one child who has Celiac (51%). Popular health professional topics to be included in a food guide were plant-based meal plans (64%), label reading (93%), and processed food nutrition label assessment (81%). Families wanted to see information on Celiac (95%) and restaurant menu selection (72%). Both groups wanted to include modules on iron intake (82%) and added sugars (80%) with school friendly recipes.

Conclusions: A Gluten-Free nutritional guide should include information on common micronutrient deficiencies seen in the diet and nutrition literacy topics such as label reading and restaurant menu selection.

Funded By: WCHRI Graduate Studentship; Trainee Travel Grant; Canadian Celiac Association

women & children's health research institute

Abstract #: 166
Presenter: Shweta V. Pipaliya
Supervisor: Joel B. Dacks
Title: Bioinformatic analyses of the ESCRT complexes in the gut parasite, Giardia intestinalis, lend insight into its enigmatic endocytic organelles
Authors: Shweta V. Pipaliya, Rui Santos, Carmen Faso, Dayana Salas-Leiva, Andrew J. Roger, Adrian B. Hehl, Joel B. Dacks
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Giardiasis is one of the most prevalent gastrointestinal illnesses in Alberta with children below the age of the 10 being the most susceptible population. *Giardia intestinalis*, the protist parasite responsible for this infection, uses its highly divergent and reduced cargo trafficking system for host gut colonization, immune system evasion, and inducing diarrheal pathophysiology throughout various points in its lifecycle. We have taken a bioinformatic approach to study the ESCRT complexes, one such trafficking machinery commonly used by pathogens for exosome biogenesis and export of virulence factors, in five *Giardia* isolates. This will allow us to better understand the molecular evolution and specific mechanisms underlying the secretory processes which greatly contribute to this organism's pathogenicity.

Methods

Recent proliferation in genome sequencing of microorganisms has allowed biologists to use the newly available data to comparatively study and identify a multitude of divergent molecular systems previously thought to be absent in pathogens. Using genomic and transcriptomic data from various free-living and parasitic relatives, we carried used comparative genomic methods, namely homology searching, phylogenetics and protein modeling, to characterize the subunits of the five ESCRT sub-complexes in *Giardia intestinalis* isolates AWB, ADH, BGS, BGS-B, and EP15. Following informatic analyses, a subunit of the ESCRTII complex, VPS25, was tagged with AlexaFluor488 and visualized by confocal microscopy to determine subcellular localization within the *Giardia* AWB trophozoite.

Results

Bioinformatic analyses allowed us to identify previously thought to be absent subunits in the *Giardia* ESCRT repertoire. These were ESCRTII-VPS36, ESCRTIII-CHMP7, and ESCRTIIIA-VPS31 and IST1. We were also able to trace molecular level differences in the encoding ESCRT proteins from the various isolates. Preliminary localization assays and fluorescence microscopy with ESCRTII-VPS25 suggested a role for this machinery at the *Giardia*-specific peripheral vacuoles, endolysosomal organelles vital for the parasite's endo- and exocytic processes.

Conclusions

Our results demonstrate that not only is *Giardia's* ESCRT complement much more complete but also that there are traceable molecular differences between the different human-infecting isolates. The current drug of choice for *Giardia* infections is a non-specific antibiotic Metronidazole to which an increase in resistance is now being observed and is on the rise. Therefore, characterization of these important protein trafficking machineries that help mediate cargo exchange and establish pathogenicity become pivotal when exploring candidates for new therapeutic targets.

Funded By: CIHR; FoMD/AHS Graduate Recruitment Scholarship, QEII Graduate Scholarship, CIHR-Canada Graduate Scholarship, NSERC Discovery Grant

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Abstract #: 167
Presenter: Jacqueline Krysa
Supervisor: Spencer Proctor
Title: Fasting Plasma ApoB-Remnant Lipoproteins Can Predict Impaired Non-Fasting Lipid and ApoB-Lipoprotein Metabolism in Healthy- and Overweight Children
Authors: Jacqueline Krysa, Donna Vine, Geoff Ball, Spencer Proctor
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Plasma apolipoprotein (apo) B-remnant cholesterol lipoproteins have been causally associated with cardiovascular disease (CVD) and ischemic-events in adults. Fasting and non-fasting plasma apoB-remnant lipoproteins are elevated in obesity and insulin resistance and contribute to early CVD risk in these conditions. Non-fasting or postprandial lipemia (or dietary fat-intolerance following a high-fat meal) includes elevated plasma triglycerides (TG) and apoB48, and fasting plasma apoB48-remnants have been shown to predict elevated non-fasting TG and apoB48 following a high fat-meal in adults. We have shown obese pre-pubertal children and adolescents with the metabolic syndrome have elevated fasting apoB48-remnant lipoproteins compared to healthy-weight youth. The aim of this study is to determine if elevated fasting apoB48-remnant lipoproteins are able to predict non-fasting apoB48 and TG in healthy-weight and overweight children.

Methods: Fasting and non-fasting plasma concentrations of apoB48 and TG were determined by SDS-PAGE and colorimetric methods following a high-fat meal (62.5% fat, 30% carbohydrates, and 7.5% protein) in healthy-weight and overweight-obese children aged 8-14 years.

Results: Our preliminary data shows fasting and non-fasting apoB48-remnant lipoproteins following a high-fat meal are elevated in overweight-obese compared to healthy-weight youth (apoB48: 8.60 ± 0.99 vs 26.42 ± 3.31, $p<0.0001$, and $apoB48_{AUC}$ 68.48 ± 9.93 vs. 262.8 ± 27.05 $p<0.001$). In addition, fasting plasma apoB48-remnant lipoproteins are highly correlated with non-fasting or postprandial response in $apoB48_{AUC}$ ($r=0.87$, $p<0.001$).

Conclusion: Our results suggest fasting plasma apoB48-remnant lipoproteins are elevated in overweight-obese youth and can predict non-fasting apoB48 concentrations in response to a high-fat meal, and these appear to be early biomarkers of exacerbated CVD risk in youth.

Funded By: WCHRI Graduate Studentship

Abstract #: 168
Presenter: Megan Jarman
Supervisor: Rhonda Bell
Title: Development of a diet quality index to assess adherence to Canadian dietary recommendations in 3-year old children
Authors: Megan Jarman, Nisha Vashi, Amy Angus, Rhonda Bell, Gerald Giesbrecht
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Little is known about the diet quality of preschool children in Canada. We adapted a previously established diet quality index for use in preschool children to align with the Canadian context and applied the index to dietary data of 1260 3-year old children to assess patterns of diet quality and associations with maternal sociodemographics.

Methods: The diet quality index (DQI) consists of 4 components which align with Canada's Food Guide (Vegetables and Fruit, Grain Products, Milk and Alternatives and Meat and Alternatives) as well as 2 less healthy components (Candy and Snacks, and Sugar-Sweetened Beverages (SSB)). A score was calculated for all 6 components, which is the ratio of each child's consumption versus the recommended intakes with a maximum score of 1 for each component. Less healthy components were reverse scored. All components were summed to give a total score between 0-6. The DQI was applied to FFQ data from 3-year old children enrolled in the Alberta Pregnancy Outcomes and Nutrition study (APrON). Scores were energy adjusted. Children were grouped into quartiles according to their total DQI score and differences in their food and beverage intakes and their mother's sociodemographic characteristics were explored.

Results: The mean DQI was 3.65±0.6. The majority of children met the recommendations for Vegetables and Fruit (73%) and Meat and Alternatives (70%), however fewer children met the recommendations for Milk and Alternatives (38%) and Grain Products (13%). There was a stark disparity in intakes of the less healthy categories, with those in the lowest quartile for DQI score consuming 82 grams Candy and Snacks and 193 grams of SSB daily. This was compared to a consumption of 45 grams/day and 17 grams/day of Candy and Snacks and SSB, respectively, in those in the highest quartile. Those who had mothers with higher levels of education and who had fewer older siblings tended to have higher DQI scores, whereas those whose mothers were obese compared to mothers who were normal weight were more likely to have lower DQI scores.

Conclusion: This DQI is useful for ranking children according to their overall diet quality. Whilst the majority of children appeared to be meeting the recommendations for Vegetables and Fruit and Milk and Alternatives, there is room for improvement for Grain Products and Meat and Alternatives. Furthermore, consumption of Candy and Snacks and SSB was common among all children and could be a target for initiatives to improve the diet quality of preschool children in Canada.

Funded By: Alberta Innovates Postdoctoral Fellowship

Abstract #: 169
Presenter: Khanh Vu
Supervisor: Anita Kozyrskyj
Title: Impact of maternal prenatal depression on infant gut microbiota and effect modification by pet ownership
Authors: Khanh Vu, Liane Kang, Tim Oberlander, Theodore Konya, David Guttman, Allan Becker, Piushkumar Mandhane, Theo Moraes, Malcom Sears, Stuart Turvey
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background

Maternal psychological distress during pregnancy is linked to allergic disease development in offspring. Experimental models of stress induce gut microbial dybisosis in young rodents. Clostridial species, which are elevated in human infants following prenatal exposure to pets, increase serotonin production in colonic cells when introduced to germ-free mice. Little is known about the impact of stress on human infant gut microbiota. This study investigated microbial taxon profiles of 4-month infant stool based on maternal depressive symptoms (DS) and serotonin reuptake inhibitor (SRI) antidepressant use during pregnancy.

Methods

This was a substudy of 1,681 term infants from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. From maternal report of prenatal medication use and DS (Center of Epidemiologic Studies Depression Scale), four groups were identified: no DS or SRI use, SRI treatment with low DS levels, only DS, and both DS and SRI use. 16S rRNA sequencing determined microbial taxon profiles in infant stool. The relative abundance of infant gut microbiota at 4 months of age was compared across the groups of DS and SRI by multivariable negative binomial model adjusted for breast feeding, infant age and maternal intrapartum/infant antibiotic use. An interaction between maternal DS and prenatal pet exposure was tested.

Results

During pregnancy, one-quarter of mothers experienced clinically-relevant DS and 4% took SRI antidepressants. Compared to infants of mothers with few DS, infants of mothers with prenatal DS +/- SRI use had higher median abundance of *Lachnospiraceae* in their gut (2.13 vs 4.62 and 3.38 %, respectively). The impact of prenatal DS and/or SRI use on *Lachnospiraceae* abundance was modified by prenatal pet ownership ($p_{interaction} = 0.02$). In the presence of pets, *Lachnospiraceae* were enriched by 28% and 30% if the mothers had prenatal DS with or without SRI treatment, respectively; and by 47% with SRI treatment but few DS. In the absence of pets, infants of mothers having DS and receiving SRI treatment have 68% lower *Lachnospiraceae* abundance than those of normal mothers. In the absence of pets and SRI use, there was no difference in *Lachnospiraceae* abundance between fetal/infant exposure to maternal DS versus not.

Conclusions

Maternal prenatal DS and/or SRI exposure may increase the abundance of *Lachnospiraceae* (from the *Clostridia* class) in 4-month-old infants, especially in the presence of pets. This change in the gut microbiota of young infants may increase their risk of allergic disease outcomes.

Funded By: CIHR

Abstract #: 170
Presenter: Dawson Lafleur
Supervisor: Eytan Wine
Title: Examining the pathogenicity of non-IgG bound bacteria in pediatric IBD
Authors: Dawson Lafleur, Jeremy Jerasi, Heather Armstrong, Eytan Wine
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Inflammatory bowel diseases (IBD) are a group of complex and multifactorial disorders with unknown etiology. We hypothesized that host immunoglobulin (Ig)G can be used to identify bacteria involved in IBD pathogenesis. In a separate project, IgG-bound and -unbound microorganisms were isolated from ileum washes of IBD and non-IBD pediatric patients. IgG binding favored specific and unique mucosa-associated species while *Pseudomonas* ST29 demonstrated reduced IgG binding in IBD patients. *In vitro* analysis of the IgGbound bacteria confirmed that they displayinvasive potential. This project has tested the reverse hypothesis that the non-IgG-bound *Pseudomonas* ST29would not display invasive potential.

Methods: Efforts to isolate *P.* ST29from patient samples were not successful. *Pseudomonas protogens* was purchased from ATCC to use as an alternative; *P. protogens* was the closest isolate available, displaying 96% sequence homology with *P.* ST29, making it an acceptable approximation of *P.* ST29*'s* behavior. HT29 intestinal epithelial cells were infected with *P. protogens, Escherichia coli* strain AIEC (positive control), and *E. Coli* strain HB101(negative control). Invasive potential was demonstrated visually using confocal microscopy and quantified using gentamicin protection assays. qPCR quantified the induction of immune markers following infection.

Results: Results from microscopy demonstrated a low level of invasiveness upon infection with *P. protogens*;AIEC was highly invasive and HB101 did not demonstrate any level of invasiveness. Following a 24-hour infection and gentamicin assay, *P. protogens* was minimally invasive, comparable to HB101; AIEC was again found to be highly invasive. Following infection, *P. protogens* elicited a minimal interleukin-6 proinflammatory response measured by qPCR, demonstrating a low level of HT29 immune activation.

Conclusions: In the context of the larger study, this work supports the hypothesis that IgG coating in pediatric IBD labels invasive and immune-activating strains of bacteria. Bacteria strains with increasedIgG-binding in IBD patients displayed increased invasive potential *in vitro. Pseudomonas* ST29demonstrated reduced IgG binding in IBD patients compared to non-IBD, and the highly homogenate isolate *P. protogens* demonstrated low invasive potential and low immune activation *in vitro.* This research demonstrates that IgG binding can be used to identify the bacteria that are important in establishing and/or exacerbating the inflammation in IBD patients. Larger studies are certainly required to confirm our findings and direct further research into novel pathobionts. Elucidating the role of specific bacterial species in IBD pathogenesis will underpin new strategies to direct therapies to those patients most likely to respond.

Funded By: NASPGHAN Foundation Mentored Summer Student Research Program, Ferring Scholarship Grant Award

Abstract #: 171
Presenter: Farah Elawar
Supervisor: David Marchant
Title: Genetic variation of Respiratory Syncytial Virus predicts virulence and efficacy of immunoprophylaxis in infants
Authors: Farah Elawar, Cameron Griffiths, Leanne Bilawchuk, Gail Porter-Lai, Carina Majaesic, Bart Hazes, Steven Drews, Asuncion Mejias, David Marchant
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background. The substantial health and financial burden of Respiratory Syncytial Virus (RSV) are recognized worldwide but effective infection management and treatment have not yet been established. We believe that this is due, in part, to an incomplete understanding of RSV transmission and virulence in the community. Therefore, we integrated next-generation sequencing (NGS) and viral replication analysis with surveillance of RSV from patients to study RSV evolution, adaptation and resistance to immuno-prophylaxis by Palivizumab (PZM).

Methods. RSV type A and type B, isolated from patients hospitalized with RSV infection, were studied over four RSV seasons (2014–2018) in Western Canada, and Ohio, USA. Correlation of patient viral titers by qRT-PCR and RSV replication kinetics in-*vitro* provided a comparison of virus titers; foci size; and replicative efficiency with the phylogenetic structure of RSV, which was determined by phylogenetic analysis of NGS data. We performed neutralization assays with patient RSV isolates and PZM (monoclonal antibody) to test for PZM resistance in the patient RSV by a colorimetric immuno-plaque assay.

Results. A clade emerged, termed high-titer (HiT) clade, that stemmed from the highest titer isolate from the previous season. InterestinglyRSV type A and type B displayed a correlation between their plaque size and their viral titer within the patient. This was indicated by a strong correlation between the viral genome and the replication ability of the virus in-*vivo*. Neutralization assays with PZM (monoclonal antibody) provided evidence for viral resistance to PZM. We observed mutations outside of the palivizumab binding site that correlated with virus resistance to PZMthat are cloned into an RSV reverse genetics system in the laboratory.

ConclusionViral genetics plays a large role in determining virus replicative capacity and resistance to immunoprophylaxis in patients. Community surveillance for HiT RSV isolates in conjunction with RSV phylogenetics may be useful to predict new clades and virulence of RSV in impending seasons.

Funded By: WCHRI Graduate Studentship; CIHR

Abstract #: 172
Presenter: Jesus Serrano-Lomelin
Supervisor: Maria Ospina
Title: Health inequality patterns in respiratory diseases during early childhood: a population-based study in Alberta, Canada.
Authors: Jesus Serrano-Lomelin, Ana Belon, Candace Nykiforuk, Maria Ospina
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Low socioeconomic status has been linked to a higher incidence of child respiratory problems. In Canada, asthma impacts 15% of children and youth, with higher hospitalization rates among those living in low-income areas or with parents with low-education levels. Health inequality patterns by socioeconomic status have not been described in detail for other childhood respiratory diseases (e.g., pneumonia, croup). Identification of these patterns can provide useful information to improve respiratory disease management during childhood. This study explores health inequality patterns by material- and social-deprivation indexes for respiratory diseases during early childhood, based on the number of hospitalizations and emergency department visits (ED-visits) that occurred from birth to five years of age.

Methods: We conducted a population-based retrospective cohort study including all singleton live births (≥ 20 weeks of gestation) born between 2005 and 2009 in Alberta. Birth data were obtained from the Alberta Perinatal Health Program. Hospitalizations and ED-visits due to a primary diagnosis of respiratory diseases (acute bronchiolitis, asthma, croup, other acute lower respiratory infections (OALRI), other acute upper respiratory infections, influenza, and pneumonia) were extracted from the Discharge Abstract Database and the National Ambulatory Care Reporting System, respectively. We evaluated inequalities in health services use according to the Pampalon material and social deprivation indexes, which rank the study population into quintiles according to six socio-economic maternal indicators: education level, income, and employment (material component); and marital status, single-parent families, and living alone (social component). We estimated concentration indexes (*CIx*) and area-level concentration curves to measure respiratory health inequalities across 25 socio-economic groups, which describe the combinations of the material and social quintiles. The first socio-economic group corresponded to the most deprived subpopulation, whereas the 25th socio-economic group refers to the least deprived subpopulation. We used STATA 13.1 to estimate *CIx* and EXCEL for area-level concentration curves graphs.

Results: The *CIx* identified negative, moderate inequalities (range between -0.20 to - 0.06) related to hospitalizations and ED-visits for most of the respiratory conditions, indicating that health services use was concentrated among the more deprived groups. A high inequality pattern was observed for hospitalization due to pneumonia (*CIx*=-0.23; 95% confidence interval [CI] -0.33, -0.13), and for ED-visits due to bronchiolitis (*CIx*=-0.21; 95%CI -0.29, -0.12) and OALRI (*CIx*=-0.22; 95%CI -0.32, -0.12). Equity was observed for croup.

Conclusions: We identified high inequality patterns based on material and social-deprivation indexes related to pneumonia, bronchiolitis, and OALRI in young children in Alberta.

Funded By: WCHRI Start-up or Retention Funding; Provincial Lung Association Grant-in-Aid Program - National Grant Review

Abstract #: 173
Presenter: Ana Paula Belon
Supervisor:
Title: The Impact of Maternal Material and Social Deprivation on the Use of Emergency Department Visits for Pneumonia and Influenza in Early Childhood
Authors: Ana Paula Belon, Jesus Serrano Lomelin, Maria-Beatriz Ospina, Candace Nykiforuk
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Material and social deprivation influences child respiratory health. Low income, education levels and unemployment have been linked to a higher incidence of child respiratory problems and emergency department (ED) visits. Missing from the literature are longitudinal studies on the association between material and social deprivation and child respiratory health. This study fills this gap by examining the impact of maternal material and social deprivation on the use of ED services for pneumonia and influenza in a birth cohort.

Methods: Population-based retrospective cohort study in Alberta, Canada. We followed-up all singleton live births (≥ 20 weeks of gestation) born between April 1st, 2005 and March 31st, 2009 until they were five years old. We obtained birth and ED-visitsdata regarding pneumonia (J12-J18) and influenza (J09-J11) from the Alberta Perinatal Health Program (APHP) and the National Ambulatory Care Reporting System (NACRS), respectively. The two components (material and social) of the Pampalon Deprivation Index were used as proxy for baseline maternal-child deprivation. The material component reflects mainly maternal education, and income, while the social component encompasses marital status, living alone, or being in a single-parent family. Results are reported in quintiles, where Q1 (reference) and Q5 correspond to the least and most deprived groups, respectively. We used Poisson regression models to estimate incidence risk ratios (IRRs) with 95% confidence intervals (CI) while adjusting for adverse birth outcomes (e.g., preterm birth), neonate sex, and adverse maternal conditions in pre-, during, and post-pregnancy. Analysis was performed in STATA 13.1.

Results: Both material and social deprivation indexes showed statistically significant effects; however, the former had a clearer gradient pattern in comparison to the latter. We found an inequality gradient in both pneumonia and influenza, with higher IRRs as the material deprivation increased. For pneumonia, the IRR in the Q5-material was 1.75 (95%CI 1.67, 1.83) versus an IRR=1.06 (95%CI: 1.01, 1.12) in the Q5-social.For influenza, the IRR was only significant in the Q5-material while the IRRs for the social deprivation had no clear pattern.

Conclusions: Material disadvantage in the mother is associated with an increased number of ED visits for pneumonia and influenza in early childhood. Public health programs should pay close attention to the exposures and health conditions of the most materially deprived groups to counteract the damaging effects of social and material disadvantage on the child respiratory health.

Abstract #: 174
Presenter: Joanne Smith
Supervisor: Gordon Chan
Title: Farnesyltransferase inhibitors enhances MK-1775 mediated cell killing.
Authors: Joanne Smith
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction:

The mitotic checkpoint is responsible for the delay of anaphase until all chromosomes are correctly aligned at the metaphase plate to ensure correct chromosome segregation. Spindly, a mitotic checkpoint protein, is recruited to kinetochores in a farnesylation dependent manner and acts an adaptor for dynein binding to kinetochores. Spindly knockdown results in prometaphase delay, alignment defects, loss of dynein kinetochore localization. The knockdown of Spindly phenocopies farnesyl transferase inhibitor (FTI) treatment suggesting that Spindly is the mitotic target of these FTIs. These findings lead to the question if Spindly expression predicts FTI sensitivity in cancer cells.

Wee1, a kinase responsible for the inhibition of Cdk1 at the G_2/M transition and when inhibited results in cells undergoing premature mitosis. We found that the combination of MK-1775 (a Wee1 inhibitor) and FTIs, both of which are currently in clinical trials for breast cancer, result in synthetic lethality in the breast cancer cell lines.

Methods:

Cell lines: MDA-MB-231 (triple negative breast cancer cell line) and HeLa (cervical cancer cell line) were obtained from ATCC.

Small Molecule inhibitors: MK-1775 (Chemie Tek); FTIs: L-744-832, FTI-277, Tipifarnib.

Cell synchronization: Synchronized in G_1/S phase by double thymidine block as previously described (Moudgil *et al.*, 2015).

Crystal Violet Assay: Cells were seeded at 1000 cells per well (HeLa) or 2000 cells/well (MDA-MB-231) and then treated with increasing concentrations of MK-1775 alone or in combination with FTI. After treatment, cells were stained with 0.5% crystal violet as outlined by Feoktistova *et al.* Absorbance at 570 nm was measured using a plate reader with the Optima software. Percent surviving attached cells was normalized to solvent control.

Colony formation: Cells were seeded as in the crystal violet assay and treated alone or in a combination of FTI and MK-1775 for 48 hours. Treatments were removed and cells were cultured for 14 days. Cells were then fixed and stained for crystal violet. Colonies were then counted.

Results:

Using colony formation and crystal violet viability assays, we have shown that FTI and MK-1775 are synthetic lethal in HeLa cells.

Conclusions:

Preliminary data indicates that the synthetic lethal relationship between FTI and MK-1775 is conserved in some breast cancer cells. Further experiments are required to confirm these results. Combination treatment of FTI and MK-1775 might represent a new treatment for selected breast cancers.

Moudgil *et al.* J Cell Biol. 2015; 208:881–896.

Feoktistova *et al.* Cold Spring Harb Protoc. 2016(4):pdb.prot087379.

The Power of Partnership

Funded By: NSERC

Abstract #: 175
Presenter: Powel Crosley
Supervisor: Mary Hitt
Title: TRAIL-expressing oncolytic vaccinia virus combined with small-molecule drug PAC1 is a potentially effective treatment alternative for ovarian cancers
Authors: Powel Crosley, Kate Agopsowicz, Kyle Potts, Ryan Noyce, Anniina Farkkila, David Evans, Mary Hitt
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Procaspase activating compound-1 (PAC1) is a small-molecule drug shown *in vitro* to sequester inhibitory zinc ions from Caspase-3. TNF-related apoptosis-inducing ligand (TRAIL) is a pro-apoptotic ligand that binds membrane-bound death receptors, triggering the extrinsic apoptotic pathway. Both agents display low toxicity in humans. Vaccinia virus (VACV) is a double-stranded DNA virus that has shown therapeutic efficacy in clinical trials and has an established safety profile in humans from its use as the smallpox vaccine.

First-line therapy for ovarian cancer is combination taxane and carboplatin, which has significant toxicity and 70% of women who receive it suffer relapse. Clinical trials involving TRAIL, both alone and combined with other drugs, have shown it is well-tolerated but is ineffective partly due to insufficient dosing at the tumour site.

In an effort to uncover a safer, more effective therapeutic for ovarian cancer we report here on the construction of an oncolytic vaccinia virus expressing TRAIL (VACV^{TRAIL}). Secretion of TRAIL by VACV-infected cancer cells will result in localized administration of TRAIL at higher dosages and minimize potential side-effects. We posit that treatment with PAC1 and VACV^{TRAIL} represents a potentially safe, effective treatment for ovarian cancers.

Results: Testing in cell line models of granulosa cell tumour (GCT) have shown that recombinant human (rh)TRAIL is effective in combination with PAC1. Dose-response assays established that combination of PAC1 (20 µM) with rhTRAIL (10 ng/mL) dramatically reduced viability of cancer cells while being substantially less toxic to normal cells. Replication of those assays on patient-derived primary and recurrent GCT cells confirmed PAC1 combined with rhTRAIL was dramatically more cytotoxic than treatment with rhTRAIL or PAC1 alone.

To optimize delivery of TRAIL to tumour cells, we constructed a recombinant VACV^{TRAIL} virus that secretes TRAIL in the range of 70–80 ng/mL. Dose-response curves showed VACV^{TRAIL} to be strongly cytotoxic with an ED_{50} of 0.1 plaque forming unit (PFU) per cell. Comparing toxicity of VACV^{TRAIL} to a non-TRAIL-expressing VACV established that secretion of TRAIL is the basis for VACV^{TRAIL} superiority in killing GCT cells, and supernatant collected from infected cells is more effective at reducing cell viability when combined with PAC1 than is rhTRAIL combined with PAC1.

Conclusion: We have successfully constructed a TRAIL-expressing oncolytic VACV that produces effective levels of active TRAIL from infected cells. Results *in vitro* suggest combining PAC1 with oncolytic VACV^{TRAIL} will allow localized delivery of TRAIL resulting in a safe, synergistic, self-amplifying therapy.

Funded By: WCHRI Innovation Grant; Granulosa Cell Tumour Research Foundation

Abstract #: 176
Presenter: Amel Hamza
Supervisor: Michael Doschak
Title: Bisphosphonate drug alveolar bone burden in Osteoporosis
Authors: Amel Hamza, David Wishart, Michael Doschak
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Osteonecrosis of the jaw (ONJ), a severe bone disorder that leads to bone death is caused mainly by nitrogen-containing bisphosphonate drugs. Recent observations suggest that the nature of ONJ is not an area of avascular necrosis, nor an osteomyelitis, but an inability of the alveolar bone to metabolically respond to stimuli. Our study hypothesis was that the identification of key metabolites involved with the pathogenesis of ONJ may serve as a diagnostic mechanism for measuring the extent of ONJ present in the bones of patients following long-term bisphosphonate therapy.

Methods: We used a metabolomics profiling approach, to observe metabolic changes in plasma and urine in an established rat model of osteoporosis, secondary to surgical ovariectomy (OVX). The commercially available Biocrates kit was used as a tool in order to provide new information on the alteration in metabolite level and to determine the potential therapeutic insight offered by metabolomics profiling following bisphosphonate drug intervention. Forty OVX rats were used in this study, and divided into four experimental groups (n=10/group), namely: Control rats dosed with vehicle, rats dosed with 0.12 mg/kg Alendronate twice weekly, third group dosed with active Vitamin D (100 ng/kg) and a combination group receiving both Alendronate and Vitamin D. Plasma and urine from the four groups of rats were collected at baseline, 4 week and 8 week study endpoint using metabolic caging, and subjected to metabolomic analysis and *in vivo* Micro CT scan measurement of bone volume.

Results: Preliminary results by micro-CT confirmed an osteopenic phenotype developing in the trabecular bone of all OVX rats. A distinct metabolite "fingerprint" was measured following drug treatment between control and treated groups, with key metabolites detected in Alendronate-dosed groups compared to the other groups. In particular, the presence of taurine, sugar, glycerophospholipid, creatinine, and acylcarnitines was in high level compared to control group.

Conclusions: These findings suggest that the use of a metabolomic approach would be of value to dentists attempting to alleviate symptoms associated with osteonecrosis of the jaw induced by bisphosphonate drug therapy.

Funded By: CIHR; The Metabolomics Innovation Centre (TMIC)

Abstract #: 177
Presenter: Mackenzie Coatham
Supervisor: Lynne-Marie Postovit
Title: Characterization of cell line models of dedifferentiated endometrial cancer and possible treatment with synthetic lethality-based approaches
Authors: Mackenzie Coatham, Zhihua Xu, Guihua Zhang, Jiahui Liu, Martin Koebel, Franco Vizeacoumar, Cheng-Han Lee, Lynne-Marie Postovit
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: While the majority of the 7500 uterine cancer cases diagnosed in Canada in 2017 were curable, approximately 15% of women still succumb to recurrent disease. One of the most lethal subsets of uterine cancer is dedifferentiated endometrial carcinoma (DDEC). DDEC tumors possess both well-differentiated and undifferentiated regions. The majority of metastatic disease is made up of cells from the undifferentiated component of DDEC. An examination of DDEC lesions revealed that 80% of the undifferentiated regions within these neoplasms lack the expression of core chromatin remodeling proteins, SMARCA4 or ARID1A and ARID1B. We hypothesize that loss of these proteins, which are known regulators of transcription, may lead to the induction and/or maintenance of stem cell-like gene expression programs that drive dedifferentiation, metastasis and therapy resistance.

Methods: SMARCA4-deficient endometrial cancer (EC) cell lines were generated by CRISPR and validated using immunofluorescence and immunohistochemistry. qRT-PCR was used to assess the level of expression of markers of epithelial-to-mesenchymal transition (EMT), stemness and endometrial lineage. The ability of the generated knockouts to proliferate, form spheres and grow anchorage-independent was evaluated. Tumor formation in immune-compromised mice was monitored to ascertain any histological differences between wildtype and SMARCA4 knockout EC cells. Finally, an examination of the response of cell line models of DDEC to inhibitors that target proteins that should promote synthetic lethality in EC cells lacking SMARCA4 expression was undertaken to ultimately find new therapeutic strategies that could improve the outcomes for DDEC patients.

Results: EC cells lacking SMARCA4 expression have significantly reduced E-cadherin and estrogen receptor levels while also possessing increased levels of the stemness associated marker, Oct4. Passaging of SMARCA4 knockout cells *in vivo* resulted in the formation of tumors consisting of both differentiated and undifferentiated regions. Inhibiting SMARCA2 or EZH2 potentially impairs the fitness of SMARCA4 deficient EC cells, a phenomenon that has been observed in other SMARCA4 deficient lung and ovarian cancers. Synthetic lethality may also be promoted in EC cells lacking SMARCA4 by inhibiting the activity of several other proteins such as cyclin-dependent kinases, DNA and histone methyltransferases and proteins within DNA damage repair pathways.

Conclusions: SMARCA4 deficient EC cell lines have been shown to partially undergo EMT and recapitulate the clinical DDEC phenotype. Determining the extent to which loss of SMARCA4 contributes to the acquisition of DDEC is a critical step towards improving diagnostic and treatment practices for aggressive stem-like forms of gynecological cancers.

Funded By: WCHRI Graduate Studentship; CIHR; Alberta Innovates

women & children's health research institute

Abstract #: 178
Presenter: Guanmin Meng
Supervisor: David Brindley
Title: Dexamethasone decreases the autotaxin-lysophosphatidate-inflammatory axis in adipose tissue: Implications for the Metabolic Syndrome and breast cancer
Authors: Guanmin Meng, Xiaoyun Tang, Yuanyuan Zhao, Jonathan Curtis, Todd McMullen, David Brindley
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

We have previously established that inflammatory cytokines from breast tumors increase autotaxin (ATX) secretion in adjacent adipose tissue. ATX produces most of the extracellular lysophosphatidate (LPA), which is dephosphorylated by lipid phosphate phosphatases (LPPs). LPA promotes a vicious inflammatory cycle by increasing the synthesis of cyclooxygenase-2 and multiple inflammatory cytokines that stimulate further ATX production. This ATX-LPA-inflammatory axis in cancers promotes tumor growth, metastasis and the loss of efficacy of chemotherapy and radiotherapy. The anti-inflammatory glucocorticoid, dexamethasone (DEX), is commonly used to decrease inflammation in the treatment of cancers. We hypothesized that DEX has an action in blocking LPA signaling in adipose tissue, which would lower the effects of the feed forward inflammatory cycle during breast cancer therapy. Our goal was to determine if DEX attenuates excessive LPA signaling and abolish adipose tissue inflammation.

Methods

We determined whether DEX functions by decreasing the autotaxin-LPA-inflammatory cycle using the cultured human adipose tissue, a major site of autotaxin secretion and the appropriate tissue model for studying the supply of ATX for breast tumors. We also verified the results in a mouse model. We assayed ATX activity, cytokines and hormones using Human Cytokine/Chemokine 64-plex ELISA or Mouse Cytokine/Chemokine 32-plex ELISA and Mouse Metabolic 11-plex arrays, qRT-PCR, and liquid chromatography/tandem mass spectrometry (LC-MS) for LPA molecular species and sphingosine 1-phosphate (S1P) concentrations.

Results

Treatment of human adipose tissue with 10-1000 nM DEX exhibited dual-effects in regulating LPA signaling, by reducing ATX production from human adipose tissue, which would decrease the synthesis of extracellular LPA; Meanwhile LPP1 expression, which terminates LPA signaling was increased. DEX also decreased mRNA expressions for IL-6, TNF-alpha, PPAR-gamma and adiponectin. Co-treatment with rosiglitazone, an insulin sensitizer, and/or insulin abolished DEX-induced decreases in ATX and adiponectin secretion, but did not reverse DEX-induced decreases in secretions of 20 inflammatory cytokines/chemokines. Moreover, DEX-treated mice exhibited lower ATX activity in the plasma, brain and adipose tissue, and decreased plasma concentrations of LPA and S1P, as well as decreased mRNA levels for LPA_1 and LPA_2 receptors and $S1P_1$ and $S1P_3$ receptors in brain and the reduced protein expressions of COX-2 and the LPA_2 receptor in adipose tissue.

Conclusions

Our results establish a novel mechanism for the anti-inflammatory effects of DEX through decreased signaling by the ATX-LPA-inflammatory axis. The glucocorticoid action in adipose tissue has implications for the pathogenesis of insulin resistance and obesity in the Metabolic Syndrome and breast cancer treatment.

Funded By: WCHRI Innovation Grant; Canadian Cancer Society Research Institute

Abstract #: 179
Presenter: Xiaoyun Tang
Supervisor: David Brindley
Title: Lipid phosphate phosphatase 2 regulating G1/S cell cycle transition in human breast cancer cells
Authors: Xiaoyun Tang, Christopher Cromwell, Rongzong Liu, Basil Hubbard, Todd McMullen, Roseline Godbout, David Brindley
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: The group of lipid phosphate phosphatases (LPPs) consists of three isoforms: LPP1, 2 and 3 which dephosphorylate varies of bioactive lipids including lysophosphatidate (LPA) and sphingosine-1-phosphate (S1P). Previous studies showed that LPP1 and 3 inhibited tumor growth and metastasis, which is related to the decrease of extracellular LPA and the attenuation of downstream signaling. However, evidence also shows elevated LPP2 levels in several cancers which promote cell proliferation. This property of LPP2 is distinct from LPP1 and 3.

Methods: We measured LPP2 mRNA level in tumors from breat cancer patients and normal breast tissue from patients receiving breast reduction surgery. We established LPP2 knockout breast cancer cells with CRISPR-Cas9 technology, and investigated the influence of LPP2 knockout on cell proliferation, cell cycle and tumor growth.

Results: The present study showed that LPP2 mRNA level was significantly higher in tumor tissues from breast cancer patients relative to normal breast tissues from non-cancer patients, which is completely different from the expression pattern of LPP1. Breast cancer patients with high expression level of LPP2 were prognostic of poor survival. Knockout LPP2 in MDA-MB-231 and MCF7 cells significantly inhibited cell growth, which is accompanied with an increase of cells in G1/0 phase and inhibition in G1/S transition. These were associated with decreases of c-Myc and cyclins and increases of cycle inhibitor p16 or p27. Tumors formed by LPP2 knockout MDA-MB-231 cells showed a 67% decrease in volume and a 68% decrease in weight relative to wild-type cells.

Conclusions: This study demonstrated that LPP2 regulates c-Myc and cell cycle, which is a potential therapeutic target for breast cancer.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant; CBCF

Abstract #: 180
Presenter: Sarah Kent
Supervisor: Dr. Jane Schulz
Title: The knowledge of pelvic floor disorders amongst Canadian immigrants
Authors: Dr. Annick Poirier, Lina Roa, Sarah Kent, Maryna Yaskina, Dr. Jane Schulz
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Urinary Incontinence (UI) and Pelvic organ prolapse (POP) are the two most common Pelvic Floor Disorders (PFD) affecting the quality of life of millions of women worldwide. Although a variety of treatments are available, women are failing to seek care. Lack of patient knowledge on these conditions has been identified as a major barrier to access treatment, particularly among non-white women as compared to white women in the United States. We aimed to assess knowledge about UI and POP amongst women in Edmonton and hypothesised that immigrant women are less knowledgeable about UI and POP than women born in Canada.

Methods: This is a cross-sectional study of women in Edmonton. Our sample size was calculated to be 100 women for each of the two study arms; immigrant women over 18 attending the Multicultural Health Brokers Cooperative (MCHB) and Canadian born women from the Colposcopy clinic at the Lois Hole Hospital for Women. The survey included the validated PIKQ (prolapse and incontinence knowledge questionnaire) and Demographic information to adjust for cofounders. Scores for UI and POP were calculated and a Mann Whitney U test was used to compared the groups.

Results: 106 immigrants and 102 Canadian born women were recruited. The mean UI score for Canadian women was 8.5 compared with 7.2 for immigrants, a statistically significant difference (p=0.005). 106 immigrants and 102 Canadian born women were recruited. The mean POP score for Canadian women was 6.0 compared with 5.6 for immigrants, not statistically different. When the overall PIKQ score was calculated, there was a statistically significant difference between both groups (p=0.04).

Conclusion: PFD has a negative impact on quality of life of a large percentage of Canadian women ranging from urinary tract infections to social embarrassment and isolation. To our knowledge this is the first study comparing knowledge of PFD in Canadian and immigrant women. Our findings suggest that in Edmonton, immigrant women have less knowledge, which is a known barrier to accessing treatment. This is consistent with literature suggesting that racial minorities have less knowledge and access. Our results will help advocate for resources and address knowledge gaps amongst immigrant by working in partnership with MCHB to ensure more immigrant women seek care for these highly prevalent, detrimental, and curable diseases.

Funded By: WCHRI Start-up/Retention Funding; Innovation Grant; Resident/Clinical Fellow Trainee Research Grant; Support services; Department of Obstetrics and Gynecolgy

Abstract #: 181
Presenter: Alynna Lirette
Supervisor: Dr. Jean-Michel Le Melledo
Title: Magnetic resonance spectroscopy investigation of GABA and glutamate in women with perimenopausal depression
Authors: Jessica Luki, Dr. Christopher Hanstock, Alynna Lirette, Dr. Tami Shandro, Dr. Katherine Aitchison, Dr. Jean-Michel Le Melledo
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: An increased risk of depression occurs in women during life events associated with fluctuations in female hormones. A third of these women present with their first major depressive episode during perimenopause. This suggests a specific pathophysiology for perimenopausal depression. The onset of perimenopause is marked by the end of menstrual cycle regularity and is associated with decreases in ovarian inhibiting hormones, increases in follicle stimulating hormone and fluctuations in female hormone levels. The perimenopause period carries a greater risk of recurrence for major depressive episodes. This risk is greater in women with a history of mood vulnerability related to female hormone fluctuations such as those with premenstrual dysphoric disorder or postpartum depression. Female hormones may play a role in the pathophysiology of depressive symptomatology through their effects on neurotransmitters such as GABA and glutamate. This study aims to identify the changes in GABA and glutamate levels in women suffering from perimenopausal depression.

Methods: During the first of two visits, participants undergo screening at the University of Alberta Hospital. This includes a medical and psychiatric history. During the second visit, participants undergo blood sampling to measure female hormones and a magnetic resonance spectroscopy (MRS) scan at the Peter Allen MR Research Centre during the follicular phase of their menstrual cycle. The MRS scan assesses the concentrations of glutamate and GABA in the medial and left dorsolateral prefrontal cortex. Participants are instructed to avoid smoking, caffeine and alcohol prior to the MRS session. Two-sample t-tests comparing patient to control groups are conducted for each variable measured. Data is analyzed using IBM SPSS statistics.

Expected Results: We anticipate GABA and glutamate levels will be altered in women with perimenopausal depression compared to perimenopausal controls.

Conclusion: Fluctuations in female hormones during the perimenopause period are associated with an increased risk of depression. Hormonal effects on neurotransmitter levels may play a role in the pathophysiology of depressive symptomatology seen in these women. The results of this study could lead to valuable information regarding the impact of hormone fluctuations on neurotransmitters, development of preventative approaches and future therapeutic strategies for women with perimenopausal depression.

Funded By: CIHR; Cranston Family Grant, FoMD - The Vessie Heckbert Memorial Summer Research Award

Abstract #: 182
Presenter: Jennifer Petrie
Supervisor: Anita Kozyrskyj
Title: Concentrations of short-chain fatty acids in infancy are associated with childhood weight
Authors: Jennifer Petrie, Sarah Bridgman, Brittany Matenchuk, Rupasri Mandal , Meghan Azad, Catherine Field, Andrea Haqq, Allan Becker, Stuart Turvey, Piush Mandhane
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

The incidence of obesity is increasing to globally consequential proportions, with 30 percent of the population affected by the disease worldwide. In children, short-chain fatty acid (SCFA) concentrations are correlated with childhood BMI z-scores. SCFAs are metabolites of the gut microbiota which impact host health through multiple pathways. Differences in fecal SCFA have been observed between normal weight and obese children, but to date, no studies have been conducted in infants. This study aimed to describe patterns of fecal SCFA concentrations in infants of the Canadian Healthy Longitudinal Development (CHILD) cohort. Additionally, associations between infant fecal SCFA and later childhood weight were examined.

Methods

Fecal samples were taken from 699 infants participating in the CHILD cohort whose mothers were enrolled between 2009-2012. Fecal samples were collected at three months of age and analysed using NMR spectroscopy. Anthropometric measurements were available for 600 children and taken at 3 years of age. Using this data children were classified as normal weight or overweight or obese (Ow+Ob). Additional infant and maternal characteristics were collected using standardized questionnaires. Nonparametric tests were used to examine the relationship between SCFA concentrations, and relative proportions, and 3-year BMI z-scores and weight status.

Results

Eighty-seven percent of the children studied at three years of age were normal weight, thirteen percent were overweight, and two percent were obese. Acetate was the most predominate SCFA (Median Concentration: 71.01; IQR: 64.01; Median Relative Proportion [RP]: 0.807; IQR: 0.195), followed by propionate (Median Concentration: 10.32; IQR: 16.08; Median RP: 0.113; IQR: 0.148) and butyrate (Median Concentration: 4.64; IQR: 9.20; Median RP: 0.054; IQR: 0.082). BMI z-score at 3-years of age was significantly associated with propionate (Spearman Rho: 0.09; $p<0.05$) and butyrate (Spearman Rho: 0.12; $p<0.01$) concentration but not total SCFA (Spearman Rho: 0.04;$p=0.32$) or acetate (Spearman Rho: 0.02; $p=0.64$) concentration. Relative proportions of acetate (Spearman Rho: -0.10; $p<0.05$) and butyrate (Spearman Rho: 0.12; $p<0.01$) were significantly associated with BMI z-score. Concentrations of total SCFA, acetate, butyrate, and propionate did not differ according to child weight status. Relative proportions of acetate were significantly different between normal weight and Ow children (0.71 and 0.69 respectively, $p<0.05$, Kruskal Wallis with Dunn post hoc test).

Conclusion

These results suggest that infant fecal SCFAs are associated with BMI z-score and obesity/overweight in childhood. Future research will examine the impact of covariates on this relationship, including breastfeeding.

Funded By: WCHRI Support services; CIHR; Alberta Innovates; HYRS Program

women & children's health research institute

Abstract #:	183
Presenter:	Jessy Azarcoya Barrera
Supervisor:	Caroline Richard
Title:	Feeding a maternal diet containing buttermilk modulates breast milk choline composition and enhances ex vivo T cell responses in lactating dams
Authors:	Jessy Azarcoya Barrera, Catherine J. Field, Susan Goruk, Yves Pouliot, Jonathan M. Curtis, René L. Jacobs, Caroline Richard
Affiliations:	University of Alberta
Research Activity:	Maternal and Infant Healthy Development

Background: Previously, we demonstrated the benefits of feeding a mixture of choline forms (phosphatidylcholine (PC), glycerophosphocholine (GPC) and free choline (FC)) during lactation on maternal immune function as compared to FC. However, it is currently unclear whether dietary sphingomyelin (SM), another form of choline, has any influence on the immune system during pregnancy and lactation. The objective of this study was to determine the effect of buttermilk, which contains high amounts of SM, on maternal immune function during lactation.

Methods: At the second week of gestation, dams were randomized to one of the three nutritionally adequate experimental diet, providing 1.9g/kg of total choline: 1-Control (100% FC), 2-Buttermilk (37% PC, 34% SM, 17% GPC, 7% FC, 5% phosphocholine) and 3-Placebo (50% PC, 25% FC, 25% GPC). At the end of the lactation period, splenocytes phenotypes, *ex vivo* cytokine production after Concanavalin A (ConA) and lipopolysaccharide (LPS) stimulation and the choline moieties from pups' stomach content (mainly reflective of the dams' breast milk), were measured.

Results: There was no differences in dams and pups' body weight among groups. Breast milk from buttermilk- and placebo-fed dams had a higher proportion of SM and PC respectively, and lower proportions of FC compared to control diet (all $p<0.05$). Moreover, buttermilk-fed dams had significantly higher production of IL-2, TNF-a and IFN-g by splenocytes stimulated with ConA, a T cell mitogen, compared to both placebo and control diets (all $p<0.05$). After LPS stimulation, feeding dams with the buttermilk or the placebo diet led to a higher production of IL-10 by splenocytes (both $p<0.05$) compared with the control diet. No significant changes were observed in the proportion and activation of immune cell types among groups.

Conclusion: Overall, our results suggest that providing a mixture of choline forms in the maternal diet modulates the breast milk choline composition and favors an anti-inflammatory response to a bacterial antigen in lactating dams. Feeding buttermilk-derived choline forms to lactating dams improves maternal immune responses to a T cell mitogen while having little effect of the proportion of immune cell types.

Funded By: Dairy Farmers of Canada

Abstract #: 184
Presenter: Andy Khuu
Supervisor: Lawrence Le
Title: Correlation between bone mineral density and ultrasound velocity: a literature review
Authors: Andy Khuu, Tho N.H.T. Tran, Lawrence H. Le
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION: Although dual-energy X-ray absorptiometry (DXA) is the current gold standard for osteoporotic assessment, it fails to examine mechanical bone properties, which are relevant to the assessment of bone quality. Axial transmission ultrasound (ATU) provides a potential alternative to measure bone elasticities. The objective of this study is to examine in the published literature the correlation between DXA and ultrasound measurements, i.e., between bone mineral density (BMD) and speed of sound (SOS).

METHODS: A literature search was performed via PubMed, Scopus, and Google Scholar. Key terms used in our search included osteoporosis, axial transmission ultrasound, dual-energy X-ray absorptiometry, and bone mineral density. Through the literature, we looked at important factors such as age, gender, population size, methods of assessment, regions of interest (ROI), equipment used, and the correlation obtained between BMD and SOS.

RESULTS: Two case studies are presented in this communication.In the first study conducted by Njeh et al (2003), a cohort of 334 women with ages 20-89y was recruited. The correlation between distal radius SOS and age obtained is r = 0.60. T-score and age show a similar trend as the best fit-line is shown to curve downwards after the age of 40.In the next study conducted by Olyszynksi et al (2016), a population of 4123 (2946 women + 1177 men) between the ages of 30-96y was recruited. The correlation obtained for distal radius SOS and femoral neck BMD is r = 0.29 using linear regression analysis.

CONCLUSIONS: SOS and BMD showed moderate correlation. Further studies with postmenopausal cohort should be conducted to validate current ATU feasibility as a complement to DXA for osteoporosis screening.

Funded By: University of Alberta

Abstract #: 185
Presenter: Mervin Burnett
Supervisor: Consolato Sergi
Title: The effect of graphene oxide on osteosarcoma, hepatocellular carcinoma, and cholangiocarcinoma
Authors: Mervin Burnett, Yasser Abuetabh, Fan Shen, Sujata Persad, Roger Leng, David Eisenstat
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Cancer is defined as the uncontrolled growth ofatypical cells and is one of the major causes of death worldwide. There has been an improvement in the survival rate for peopleaffected by cancer, thanks to the advancements made in diagnosis and treatment. However, there is a need for improved management ofcancer, as traditional therapy approaches are limited by a lack of specificity and systemic toxicity. Nanoparticles with anti-cancer properties such as graphene oxide can provide an effective treatment for cancer as it can specifically target cancer cells while reducing undesired side effects. We hypothesized that graphene oxide has a toxic effect on human cancer cells while not affecting non-cancerous cell lines. This study aimed to evaluate the toxicity and underlying mechanism of graphene oxide on osteosarcoma, hepatocellular carcinoma,and cholangiocarcinoma cell lines.

Materials and Methods: Human osteosarcoma cell lines, U2OS and SAOS2; normal osteoblast cell line hFOB1.19; hepatocellular carcinoma cell line, Hep G2 and human cholangiocarcinoma cell lines OZ, HuCCT1 and Huh-28 were used. The cells were cultured in the appropriate medium and treated with graphene oxide at concentrations of 0, 25 and 50 ug/ml for 24 hours and 48 hours. Apoptosis was analyzed using the Annexin V-FITC apoptosis detection kit and Muse cell analyzer. Morphology of the cells was investigated using an Olympus camera attached to an inverted microscope. Western blotting was used to analyze for the expression of the NRF-2 antibody.

Results: There was an increase in apoptosis detection for cells treated with graphene oxide compared to the corresponding untreated cells, with a higher rate of apoptosis in the cancer cell lines than the noncancer cell line hFOB1.19. Morphologically, the hepatocellular carcinoma and cholangiocarcinoma cell lines were more affected than the osteosarcoma cell lines. Minimal morphological changes were seen in hFOB1.19 cells. Nrf-2, a transcription factor that protects against oxidative damage was highly expressed in Hep G2 and HuH-28 at both 68kDA and 100 kDa. Expression of nrf-2 was lower in the other cell lines with expression only at 100kDA.

Conclusion: The biological properties of graphene oxide make it a potential treatment option for tumor cells including osteosarcoma, hepatocellular carcinoma,and cholangiocarcinoma. Graphene oxide has a more significant effect on inducing apoptosis in cancer cell lines than in noncancer cell lines.

Funded By: WCHRI Partnership resources

Abstract #: 186
Presenter: Jennifer Mateshaytis
Supervisor: Sophia Pin
Title: A predictive model for postoperative venous thromboembolism in patients with endometrial cancer
Authors: Jennifer Mateshaytis, Sophia Pin, Sunita Ghosh, Eugene Batuyong, Jay Easaw
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction:

The association between malignancy and venous thromboembolism (VTE), and the clinical implications of VTE are well founded in the literature. In this study we report on VTE in endometrial cancers patients with three objectives: (1) to characterize the incidence of and identify risk factors for VTE, (2) to create a predictive model and risk score for VTE, and (3) to compare survival outcomes for patients with and without VTE.

Methods:

A retrospective chart review was performed; eligible patients underwent surgery for endometrial cancer at the Foothills Medical Center (01/01/2014 - 07/ 31/2016). The exclusion criteria were: benign pathology, non-gynecological primary malignancy, cases of recurrence and known VTE prior to surgery. Patients were followed from surgery to the first symptomatic VTE event, death or 180 days from the index date, whichever came first. Endpoints included: demographics, pathology, surgical details, VTE, lab work, chemotherapy, and survival. The primary outcome was postoperative VTE. Statistics were analyzed via SAS software. Binary logistic regression identified risk factors for VTE; significant risk factors were considered for the multivariate model. Based on the final model, risk factors were used to compute a risk score.

Results:

The incidence of VTE in this study was 6.54%. Clinical variables significantly related to the risk of VTE include: Ca 125, albumin, stage 3&4 disease, high grade histology, length of stay, and laparotomy. The multivariate predictive model included non-endometrioid histology, stage 3&4 disease and hypoalbuminemia ($p<0.05$) (c-statistic 0.844). Having ≥1 risk factor dramatically increased the likelihood of postoperative VTE. Survival probabilities for patients with and without a VTE were compared: 75.2% vs 96.2% at 12 months, and 61.3% vs 91.6% at 24 months. Overall death rate for postoperative endometrial cancer patients with a VTE was 33.0% (versus 6.64% without a VTE). This equates to a ~5-fold increased risk of death in the VTE group: HR 5.4, p-value <0.0001, 95% CI (2.9 – 10.3).

Conclusions:

A method to identify endometrial cancer patients at high risk for VTE is important given the implications of VTE on patient outcomes. These high risk patients may benefit from extended VTE prophylaxis. Our predictive model and risk score may be the initial step to identifying high risk patients, and reducing variability in postoperative prophylaxis practice. We intend to validate these results with data from patients treated in Edmonton.

Abstract #: 187
Presenter: Eugeniu Jantuan
Supervisor: Consolato Sergi
Title: Autophagy in cardiac myxoma
Authors: Eugeniu Jantuan, Bonnie Chiu, Brian Chiu, Gavin Oudit, Consolato Sergi
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction. Cardiac myxoma is a rare primary neoplasia. Although asymptomatic and usually discovered incidentally, it may cause embolization, heart failure, and sudden death. Cardiac myxoma is characterized by myxoma cells with an endothelial phenotype in a myxoid stroma. Composite tumors of cardiac myxoma and the associations of cardiac myxoma with lymphoproliferative disorders (LPD) have recently been reported. Chronic inflammation in response to viral infection has reportedly played a role in their development. We previously focused our attention on autophagy and inflammation interplay in heart failure. In the current study, we aimed to investigate the role of autophagy in cardiac myxoma and the tumor microenvironment.

Methods. A series of 27 formalin-fixed and paraffin-embedded human cardiac myxomas were retrieved from files of University of Alberta Hospital over a 6-year period, 2010-2016. A histological and immunohistochemical study was performed using antibodies against Beclin-1 (ab55878, 1:200 dilution; Abcam), LAMP-1 (ab24170, 1:1000 dilution; Abcam), LC3 (ab63817, 1:200 dilution; Abcam), and p62 (ab56416, 1:1000 dilution; Abcam), as well as LMP1 and Epstein-Barr virus in situ hybridization (EBER). We examined 3-4 micrometers-thick sections for the presence of Beclin-1, LAMP-1, LC3, and p62 positive cells and EBER.

Results. Three histological patterns of cardiac myxoma we described: cell, chord-like, and predominant vasoformative patterns. Complex tumor environment changes were demonstrated in all cases, varying from scattered single immune-inflammatory cells to marked chronic inflammation. The autophagy markers were highly expressed not only in the tumor cells but also in the stromal cells. Beclin-1 was positively expressed in 23 out 27 cases (85.1%), LC3 in 24/27 (88.8%), and LAMP1 was highly expressed in 25/27 cases (92.5%). Eight cases of cardiac myxoma were stained for p62 antibody and all stained positively. Two cardiac myxomas showed LMP-1 positivity, although EBER was negative.

Conclusion. Our initial findings help to speculate that autophagy dysregulation supports cardiac myxoma tumorigenesis and may create a favorable environment for the development of lymphoproliferative disorders.

Funded By: University of Alberta Hospital

Abstract #: 188
Presenter: Renee Dicipulo
Supervisor: Andrew Waskiewicz
Title: The role of Taz in zebrafish ventricle development
Authors: Renee Dicipulo, Lyndsay Selland
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Improper brain ventricle morphogenesis and the inability to regulate cerebrospinal fluid (CSF) are associated with congenital neurodegenerative defects, including hydrocephaly, which is characterized by an abnormal buildup of CSF and cognitive impairment. Although several studies have elucidated processes in ventricle development, our goal was to identify specific signalling pathways involved and the genes required for proper formation of the brain ventricle system. Our work has demonstrated a significant role for Taz, a transcriptional co-regulator canonically involved in the Hippo signalling pathway, in regulation of brain ventricle formation. Mechanistically, Taz acts as an integrator of WNT and NOTCH signaling pathways..

Methods

To understand the roles of Taz in brain ventricle development, CRISPR-Cas9 mutagenesis was used to generate zebrafish *taz* knockouts. Transgenic zebrafish lines and fluorescence microscopy were used to visualize structures within the brain and signalling pathway outputs. In situ hybridization (ISH) and Taz immunohistochemistry were used for gene expression and protein localization studies. Pharmacologic modulation of WNT and NOTCH pathways was used to determine if Taz is a component of either signaling cascade.

Results

Zebrafish *taz* mutants display significant defects in brain ventricle formation, with embryos failing to undergo midline separation, the first step of ventricular morphogenesis. Molecular studies demonstrated that Taz protein is localized to the rhombomere boundaries in a WNT-dependent manner. *taz* mutants displayed altered apicobasal polarity and absence of midline actin localization. Our studies have also indicated that chemically antagonizing the Wnt pathway phenocopies *Taz* mutants. While disruption of Notch signalling through antagonists did not result in significant defects to brain ventricle formation, or midline separation defects similar to *Taz* mutants, a reduction in ventricle size was seen, suggesting that Notch signaling is perhaps a downstream effect of altered Taz function. Consistent with this model, we observe a dramatic reduction in *rfng* expression in *taz* mutants. Current work is focused on elucidating the role of Notch in brain ventricle development.

Conclusions

We have demonstrated that *taz* is required for development of the brain ventricle in zebrafish. We propose a model in which Taz is regulated by WNT signaling and regulates cell behaviours by controlling actin dynamics and NOTCH signaling.

Funded By: WCHRI Innovation Grant; CIHR

Abstract #: 189
Presenter: Jonah Elke
Supervisor: Sandra A. Wiebe
Title: Please Stand By: EEG and behavioral correlates of delay frustration in early and middle childhood
Authors: Jonah Elke, Diya Shi, Aamena Kapasi, Sandra A. Wiebe
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

The transition to school reflects an important time in children's socioemotional development, presenting many new challenges and frustrations. To examine children's frustration regulation abilities, we had 36 4- and 5-year-olds and 28 7- and 8-year-olds complete a delay-frustration flanker task (DeFT) while their electroencephalogram (EEG) was recorded. In the DeFT, children responded according to the direction of a central target fish, ignoring congruent, incongruent, or neutral distractors. In the first (Baseline) and third (Recovery) blocks, feedback was provided after each response. In the second (Frustration) block, the computer appeared to malfunction, introducing a 2-10 second delay between the response and feedback on 25% of trials. We examined emotion-regulation-related behaviors during delays, task performance, and EEG oscillations in the alpha and theta bandwidth ranges, thought to reflect attention and cognitive control, respectively. Behaviorally, older children engaged in more self-comforting behaviors than younger children did. The Recovery block was associated with greater alpha and theta power in both age groups. Examining trials around delays, children responded to trials following delays more slowly, and children's EEG contained less alpha power in these trials. Overall, our results suggest that both 4- to 5-year-olds and 7- to 8-year-olds may respond to delay-frustration by disengaging their attention and engaging cognitive control at a global level, and by increasing their attention proximal to the frustrating event. Although older children engaged in more self-comforting, this regulation strategy did not result in significant age differences in neural or task performance.

Funded By: NSERC

women & children's health research institute

Abstract #: 190
Presenter: Aamena Kapasi
Supervisor: Jacqueline Pei
Title: The Impact of a Targeted Self-Regulation Intervention on Inhibition Among Adolescents with FASD
Authors: Aamena Kapasi, Jacqueline Pei, Tim Oberlander, Katherine Flannigan, Gail Andrew, Kaitlyn McLachlan, Sandra Hodgetts, Carmen Rasmussen
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Objective: We examined whether a self-regulation intervention demonstrated improvements in inhibition in adolescents with Fetal Alcohol Spectrum Disorder (FASD). FASD is a neurodevelopmental disorder that occurs as a result of prenatal alcohol exposure. Difficulty with inhibition, which is the ability to stop an automatic response, is one of the cognitive deficits individuals with FASD commonly experience. Improving inhibition is critical as it allows individuals to resist making impulsive comments and decisions, suppress irrelevant information, and withstand distraction from external stimuli. Inhibition is a core component of self-regulation, which involves being able to manage thoughts, impulses, and emotions, and helps individuals stay calm and focused.

Method: In this study, a self-regulation program was adapted and conducted individually with 24 adolescents with diagnosed FASD (Mage=14 years, range=11-17; 14 females). The study was conducted in hospital settings in Edmonton and Vancouver. Using a waitlist control design, participants completed pre- and post intervention testing, including three different measures of inhibition: 1) Whack-A-Mole computer task, which is a go/no go measure, 2) DKEFS colour-word interference (CWI), an established measure of inhibition, and 3) the Behaviour Rating Inventory of Executive Function, a parental report of behavioural indications of inhibition.

Results: Independent samples t-tests were conducted to compare changes in scores between the intervention group with the waitlist group, and paired samples t-tests were conducted to compare pre-and post intervention outcomes. Standard scores from the DKEFS CWI inhibition task and inhibition/switching task, T-scores from the BRIEF Inhibition scale, and total hits as well as commission errors on the Whack-A-Mole task were all used in analyses. No significant group differences were found on any measure of inhibition between the pre- and post test, or between the intervention and waitlist control group (ps>0.05). However, when examining individual participant changes, 71% of participants improved by half a standard deviation or more on at least one measure of inhibition.

Conclusion: The majority of the participants in the adapted self-regulation intervention did show meaningful improvements on inhibition. Although group-level differences were not found, it is critical to understand individual level changes in intervention research, and further investigate the differences in observed outcomes. Exploring ways to improve inhibition in adolescents with FASD allows for the development of more effective intervention initiatives that may help adolescents with FASD increase self-regulation, and ultimately contribute to reducing the risk of adverse outcomes common in the FASD population.

Funded By: WCHRI Graduate Studentship, Kids Brain Health, the Glenrose Hospital Foundation

Abstract #: 191
Presenter: Mahdieh Khodaei
Supervisor: Edmond Lou
Title: A pilot study to validate a novel method to predict progressive cases on children with Adolescent Idiopathic Scoliosis (AIS)
Authors: Mahdieh Khodaei, Rui Zheng, Thanh-Tu Pham, Lawrence H Le, Edmond Lou
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Adolescent Idiopathic Scoliosis (AIS) is a 3D spinal deformity. The standard method to measure the severity and monitor progression of scoliosis is the Cobb angle which is measured on radiographs. However, for non-progressive cases radiographs are in retrospect unnecessary. Taking radiographs expose patients to ionizing radiation which is associated with increased cancer risk. Literature has reported that 27-38% of children with AIS have been identified with osteopenia or low bone mineral density, which are associated with higher risk of curve progression. Our team has proposed a novel approach to measure bone quality in the spine area using ultrasound (US) to predict curve progression. In a pilot study, 86 participants who have AIS were scanned with ultrasound, we found that for those who had frequency amplitude index (FAI) (a value related to bone quality) ≤101.2 dB and their major Cobb angle ≥25°, their progression rate was 89%. This study was to validate our preliminary hypothesis that the FAI and Cobb angle values were highly correlated to curve progression on children with AIS.

Methods

Five-hundred female children with AIS were aimed to scan and recruit for this validation study. Currently, only 29 participants were recruited and met our inclusion criteria: need 2 consecutive clinical visits with US scan, were analyzed. All subjects were scanned in standing position by using US and had their radiographs taken on the same day. The frequency amplitude index (FAI) which reports the bone quality was extracted from the US data. The difference of the Cobb angle ≥6° between the two consecutive visits is considered curve progression.

Results

The age of the 29 subjects was 14.7±1.5 years old. Their major Cobb angles at the 1st and 2nd visits were 25.1±8.1, and 26.0±10.0 degrees, respectively. The Mean±SD of the FAI for the first visit was 100.7±1.1 dB. Among the 29 subjects, 9 participants had FAI ≤101.2 dB and their major Cobb angle ≥25°. Of these nine subjects, only three (33%) subjects showed progression ≥6°. To compare with our pilot study, the rate of progressive case was lower. However, some subjects who were under treatment had not been removed from the analysis.

Conclusions

This study showed the FAI and the severity of curvature has only 33% accuracy to predict the curve progression. However, since the number of subjects was small, more subjects are required prior to make a conclusive statement.

Funded By: WCHRI Graduate Studentship

Abstract #: 192
Presenter: Jeff Bachman
Supervisor: Rhonda Rosychuk
Title: Modeling coarsened recurrent event data from administrative databases
Authors: Jeff Bachman, Rhonda Rosychuk
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Motivated by an administrative health data set for emergency department (ED) visits made by children and youth in Alberta for mental health reasons (PMH data set), this project presents and applies a method for analyzing recurrent event data that feature coarsened event and subject-specific censoring times, events of varying duration, and periods not at risk.

Methods

In the PMH data set, the doubly censored recurrent events take place on an age time scale, and the event and censoring ages are coarsened due to the lack of birth dates. The PMH data set combines information on ED visits, hospital stays, and health care registration information from the Ambulatory Care Classification System, the Alberta Health Care Insurance Plan (AHCIP), and the Discharge Abstract Database. Subjects are not at risk while in ED or in hospital and while not registered with the AHCIP.

We apply our method to the PMH data set to fit various Cox models for repeated ED episodes and assess the impact of gender, location (rural or urban), and a proxy for socioeconomic status (pSES) on ED episode intensity. The impact of the coarseness of the data is assessed by inferring two sets of potential birth dates for each subject, one wider and one narrower, fitting the Cox models under both sets, using our method, and comparing the results.

Results

Across numerous fits, we found that gender had a strong, but non-proportional, impact on ED episode risk, showing an age-dependence effect. While young boys are at increased risk compared to young girls, teenage girls show increased risk over teenage boys. Generally, pSES had a stronger effect than rural/urban location, with those receiving social assistance at higher risk than others, and urban subjects at slightly higher risk than rural subjects.

While data coarseness has the potential for significant impact, we found minimal impact in the PMH data set. The impact increased slightly when repeating the fits on a 5% simple random sample of the subjects.

Conclusions

Our work has demonstrated that coarsened data do not necessarily result in poor estimates. While our method for dealing with missing data is motivated by the PMH data set it can be applied more generally to cases of coarsened event and censoring times, when it is possible to infer or assume appropriate distributions for the event and censoring times.

Funded By: CIHR; NSERC

Abstract #: 193
Presenter: Lu Kun Chen
Supervisor: Joseph Casey
Title: Working towards a structure of SLC4A11, a membrane protein defective in corneal dystrophies
Authors: Lu Kun Chen , Katherine Badoir, Joseph Casey
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction/Objectives

The membrane protein, SLC4A11, maintains osmotic balance in the cornea. Mutations in SLC4A11 impair this process, leading to corneal dystrophies, namely congenital hereditary endothelial corneal dystrophy (CHED), Harboyan Syndrome (HS), and Fuchs endothelial corneal dystrophy (FECD). SLC4A11 point mutations associated with disease are found in both the membrane domain (MD) and the cytoplasmic domain (CD). One catalytically inactive mutant R125H lies in the CD. This suggests a role for the cytoplasmic domain in transport function, which is not conserved in other members of the SLC4 family. The exact role of the SLC4A11 CD, and how it interacts with the MD to facilitate transport, is unknown. An SLC4A11 homology model, on the basis of SLC4A1 (Band 3) whose structure is known, provides structural approximations for the MD but does not extend to the CD.

Methods/Approach

We hope to use Cryogenic Electron Microscopy to better understand SLC4A11 structure and function in context of the full-length protein. This imaging technique requires purified protein samples. Insertion of affinity tags onto SLC4A11 allows the protein to be purified using affinity chromatography. We introduced C-terminal high-affinity epitope tags Rho and 8xHis onto wild-type SLC4A11.

Results/Findings

The Rho-tagged construct expressed to the same level as the untagged positive control. The 8xHis-tagged construct, however, expressed to a significantly lower degree than wild-type. Further, the Rho-tagged construct had more mature glycosylated product whereas the 8xHis-tagged construct contained predominately immature forms.

Conclusions

Moving forward, we will use the Rho construct to proceed with purification steps and finally, Cryogenic Electron Microscopy. Obtaining a high-resolution structure of the protein will clarify the role of the CD in water transport, and ultimately the role of SLC4A11 in causing corneal dystrophies.

Funded By: Alberta Innovates Health Solutions Summer Studentship

Abstract #: 194
Presenter: Tehzeeb Sayed
Supervisor: Edmond Lou
Title: A new kyphosis measurement method on sagittal radiographs – A pilot study
Authors: Tehzeeb Sayed, Edmond Lou
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Adolescent idiopathic scoliosis (AIS) is a three-dimensional lateral spinal deformity affecting girls aged 10 to 16 and has unknown causes. Thoracic hyperkyphosis, an excessive convex curvature of the spine when viewed laterally, is present in up to 50% of AIS cases. The gold standard measurement is from lateral radiographs using the Cobb technique by using the superior endplate of the T1 vertebra and the inferior endplate of the T12 vertebra. However, children with AIS are also repeatedly exposed to radiation over the course of their treatment. Our group developed a non-ionizing ultrasound method to accurately measure the scoliosis curve, but it cannot yet apply to the measurement of the kyphosis curve due to a lack of visible vertebral endplates. Since the spinous process is identifiable in ultrasound images, we proposed a new method based on the identification of the spinous process to measure the kyphotic angle. This pilot study was used to validate a new proposed method to measure kyphotic angle on radiographs first. Once validated, the ultimate goal is to apply this method on ultrasound images.

Methods: Fifty children with AIS were recruited with proper consent. All participants had the posteroanterior and lateral radiographs and ultrasound images acquired on the same day. Two raters, R1 (novice) and R2 (20+ years of experience) used a) the traditional Cobb method and b) the proposed spinous process method to measure the kyphotic angle. The spinous processes of T1 and T2 vertebrae are connected via a line. This is repeated with T11 and T12. The angle created at the intersection of the extension of these two lines is the new kyphotic angle (α').

Results: The intra-rater reliability (ICC [2,1]) of the new method for R1 and R2 were 0.73 and 0.98, respectively. The inter-rater reliability (ICC [2,1]) was 0.80. The mean absolute difference between R1 and R2 of the new method kyphotic measurement was 5°±5°. The average difference between the Cobb and the new methods of R2 measurements was -3°±4° and the correlation was 0.87. The spinous method always over estimated the kyphotic angle when compared with the Cobb method.

Conclusions: There was a strong correlation between the proposed spinous process method and the Cobb method. The measurement difference was within 5° of acceptable clinical error for an experienced rater. Future work includes validating this method on ultrasound images to ascertain that complete three-dimensional spinal parameters can be obtained from ultrasound images.

Funded By: Edmonton Orthopaedic Research Society

Abstract #: 195
Presenter: Joshua Kennedy
Supervisor: Jackie Whittaker
Title: Scared to move: Kinesiophobia following youth sport-related knee injuries
Authors: Joshua Kennedy, Christina Le, Jackie Whittaker
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Kinesiophobia (fear-of-movement) is associated with physical inactivity and is the most common reason for quitting sports following a serious knee injury. Currently, little is known about kinesiophobia in the acute injury stage and whether it manifests beyond the injured joint. This research assessed the relationship between self-reported kinesiophobia and bilateral knee strength or dynamic knee balance between youth within three-months of a sport-related knee injury and uninjured age-, sex-, and sport-matched controls.

Methods: Participants included 21 youth (11-19 years) who suffered a sport-related knee injury within the previous three-months and 21 uninjured age-, sex-, and sport-matched controls. Outcomes included: Tampa Scale for Kinesiophobia (TSK), normalized bilateral knee extensor and flexor isokinetic strength (Nm/kg; isokinetic dynamometer), bilateral triple-single-leg hop (TSLH), and bilateral Y-balance (YBT) test scores. Descriptive statistics [median (range), proportion or mean within-pair difference (95%CI)] were calculated for all participant characteristics and outcomes by study group. Unadjusted conditional (matched-pair) logistic regression was used to assess the odds of TSK score >37 by study group (odds ratio; 95%CI) and multivariable regression (95%CI) was used to examine the association between TSK score and each outcome, adjusting for injury history.

Results: The median age of participants was 17 years (range 16-20) and 57% were female. The median time between injury and testing was 1.5 months (range 0.3-3.4). The injured group scored higher on the TSK [mean within-pair difference (95%CI); 8 (3,13)], demonstrated weaker index (injured) leg knee extensor [-0.99 Nm/kg (-1.97,-0.02] and flexor strength [-0.96 Nm/kg (-1.85,-0.06)], and had a 10-fold (95%CI 1.3,78.1) greater odds of a TSK score >37 compared to the uninjured group. A significant association was demonstrated between TSK score and index knee extensor strength [β=-0.1 (95%CI -0.2,-0.04), r^2=0.278, p=0.01], non-index knee extensor strength [β=-0.1 (95%CI -0.2,-0.01), r^2=0.210, p=0.04], index knee flexor strength [β=-0.08 (95%CI -0.1,-0.01), r^2=0.287, p<0.01], and non-index knee flexor strength [β=-0.07 (95%CI -0.1,-0.01), r^2=0.243, p=0.03], regardless of injury group. No associations were found between TSK and TLSH or YBT scores.

Conclusions: These preliminary findings suggest that kinesiophobia may be present as early as three-months following a youth sport-related knee injury. Additionally, kinesiophobia (as measured by the TSK) seems to manifest beyond the injured joint as observed as a reduction in bilateral knee extensor and flexor strength. Further investigation is required to confirm these findings and understand the mechanisms underlying kinesiophobia to inform treatment strategies following a youth sport-related knee injury.

Funded By: University of Alberta Undergraduate Research Initiative Studentship, and Arthritis Society Young Investigator Operating Grant.

Abstract #: 196
Presenter: Jacqueline Eberhardt
Supervisor: Eric Parent
Title: The immediate effect of daily living postures on spinal curves and rotation in adolescent idiopathic scoliosis
Authors: Jacqueline Eberhardt, Eric Parent, Mathew Shaker, Edmond Lou, Alex Su
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Adolescents with Idiopathic Scoliosis (IS) spend most of their day performing activities of daily living (ADLs). Curve magnitudes can be analyzed using non-invasive 3D Ultrasound (3DUS) imaging to recommend postures that optimize spinal alignment to prevent curve progression.

The objective was to determine the immediate effect of ADLs on the curve magnitude of adolescents with IS compared to standing.

Methods: Participants were recruited from the Edmonton Scoliosis Clinic with Cobb angles of 10-45°, aged 10-18, and with right thoracic, left lumbar double curves. Their spine was scanned immediately after adopting the position via 3DUS in 18 positions: standing, model, sitting (natural, cross-legged, criss-cross, leaning forward and sideways on a table), lunge, wearing a backpack and shoulder bag, and side-sitting. Right (R) and left (L) positions were measured where applicable.

A trained evaluator used custom software, digitizing the center of lamina, to measure axial vertebral rotation (AVR), and thoracic and lumbar curve angles. A positive angle denotes a right curve (negative = left). Repeated measures ANOVA and Least Significant Difference pairwise comparisons detected significant differences between positions.

Results: Eight females aged 13.3±0.7 years were included. Mean thoracic and lumbar curve angles and AVR were 20.8±1.4°, -19.6±1.7°, and 14.4±1.3°, respectively, for natural standing.

There were significant reductions ($p<0.05$) in thoracic curve, lumbar curve, and AVR in ModelL (7.9±1.8°, -9.4±1.5°, 8.6±1.8° respectively), Sit-CrossedR (14.2±1.6°, -11.9±2.6°, 10.4±1.0°), and Sit-LeanL (4.3±2.1°, -9.4±3.7°, 8.4±1.0°) compared to standing. Thoracic and lumbar curves were also significantly reduced in Natural Sitting (12.9±2°, -11.9±2.6°), Sit-Criss-crossR (12.0±1.5°, -13.2±1.3°), Sit-criss-crossL (11.5±2.4°, -12.3±4.0°), LungeL (11.9±1.5°, -6.6±1.9°), and Bag (12.5±2.0°, -12.4±2.1°) compared to standing. Thoracic curves and AVR were significantly reduced in Side-SittingL (-1.0±1.9°, 6.7±1.7°) compared to standing. Further, Sit-Lean (13.5±2.0°) and LungeR (10.4±1.6°) significantly reduced thoracic curve compared to standing. The lumbar curve was significantly improved in Sit-CrossedL (-13.6±1.6°) and Side-SittingR (9.1±3.0°) compared to standing.

Thoracic curve and AVR were significantly reduced in ModelL (7.9±1.8°, 8.6±1.8°) compared to ModelR (22.2±2.9°, 15.9±1.3°), and in Sit-LeanL (4.3±2.1°, 8.4±1.0°) compared to Sit-LeanR (18.0±3.5°, 13.9±1.7°). Sit-LeanL (4.3±2.1°, 8.4±1.0°) also had significantly reduced thoracic curves and AVR compared to Natural-Sitting (12.9±2.0°, 11.8±0.9°)

Sit-CrossedR (10.3±1.0°) had significantly reduced AVR compared to Sit-CrossedL(12.3±0.9°).

The thoracic and lumbar curves were significantly reduced in Side-SittingL (-1.0±1.9°, -27.5±2.8°) compared to Side-SittingR (19.4±1.4°, 9.1±3.0°).

Conclusion: Positions that significantly reduced thoracic and lumbar curve angles and AVR can be recommended to maintain spinal alignment during activities of daily living.

Abstract #: 197
Presenter: Tejal Aslesh
Supervisor: Toshifumi Yokota
Title: Efficacy of CRISPR/Cas9-mediated NHEJ for the treatment of Spinal Muscular Atrophy
Authors: Tejal Aslesh, Rika Maruyama, Toshifumi Yokota
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Spinal muscular atrophy (SMA) is caused by a loss of survival of motor neuron 1 (*SMN1*) gene leading to insufficient SMN protein production and death of motor neurons. SMA is the leading genetic cause of infantile death. The *SMN2* gene is a paralog of *SMN1*; however, only 10% of the protein produced by *SMN2* is functional because of a C-to-T transition in exon 7, converting a splicing enhancer into a silencer site, which facilitates the spliceosomal machinery to exclude exon 7 in SMN2 mRNA. A promising target to treat SMA is a unique silencer sequence called intronic splicing silencer N1 (ISS-N1), a 15 nt sequence located downstream of exon 7. ISS-N1 has a strong inhibitory effect on *SMN2* exon 7 inclusion and therefore deletion of ISS-N1 can lead to splicing correction of the *SMN2* gene. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system along with CRISPR-associated protein (Cas) is now being used for genome editing to rectify genetic defects and has shown to ameliorate the pathophysiology in various genetic disease models. Similarly, the CRISPR/Cpf1 system efficiently restored SMN protein production in induced pluripotent stem cells (iPSCs) derived from SMA patients *in vitro*; however, homology-directed repair (HDR)-based method is not efficient in vivo. Here, we employed the CRISPR and non-homologous end-joining (NHEJ) system, which can be promising to induce SMN expression permanently and prevent possible side effects involved in repeated invasive injections in other therapies.

Methods: SMA patient fibroblasts were transfected with guide RNAs (gRNAs) designed to disrupt the ISS-N1. The endonuclease SpCas9 was complexed with the gRNA using a ribonucleoprotein (RNP) which increases resistance and efficiency in cells. Genomic DNA and RNA were collected post-transfection. The efficiency of the gRNAs to cleave the gDNA was tested by T7 endonuclease assay. The efficiency of exon 7 inclusion was evaluated by performing an RT-PCR on the isolated RNA. SMN protein restoration was quantified using Western blots.

Results: We identified several highly efficient gRNAs targeting the ISS-N1 and surrounding regions as detected by T7 endonuclease assay. In addition, we show that 2 gRNAs coupled with Cas9 efficiently create DNA deletions of the ISS-N1 region through the non-homologous end-joining (NHEJ) pathway.

Conclusion: NHEJ-mediated CRISPR/Cas9 editing can permanently delete the ISS-N1 and block its inhibitory function. Our findings suggest great potential for CRISPR-mediated genome editing approaches for the treatment of SMA.

Funded By: WCHRI Innovation Grant; Slipchuk SMA Research Foundation Research Grant:

Abstract #: 198
Presenter: Kenji Rowel Lim
Supervisor: Toshifumi Yokota
Title: Development of antisense gapmers to knock down DUX4 expression as a therapy for facioscapulohumeral muscular dystrophy
Authors: Kenji Rowel Lim, Rika Maruyama, Hunain Khawaja, Takako Jones, Peter Jones, Yi-Wen Chen, Toshifumi Yokota
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction. Facioscapulohumeral muscular dystrophy (FSHD) is the third most common genetic neuromuscular disorder worldwide, with a prevalence of ~1:8000-1:22000. It is an autosomal dominant disorder characterized by progressive muscular deterioration in the face, shoulders, and arms, spreading downward in the body with age. FSHD typically starts presenting in childhood; earlier manifestations are associated with increased disease severity. **There is no cure for FSHD.** Aberrant muscle expression of the *DUX4* gene, which is normally only expressed during early development, causes FSHD. This study aims to develop locked nucleic acid (LNA) and 2'-*O*-methoxyethyl (2'-MOE) gapmer-type antisense oligonucleotides to reduce *DUX4* expression in muscle, to serve as a therapeutic for FSHD. Gapmers selectively bind and degrade target mRNAs by a sequence-guided, RNaseH1-mediated mechanism, making them a suitable tool for *DUX4* knockdown.

Methods. Seven LNA and three 2'-MOE gapmers were designed against various regions of the *DUX4* mRNA and transfected into immortalized FSHD patient-derived muscle fibers, after which total RNA was collected. qPCR was used to evaluate changes in expression of *DUX4*, its downstream activated targets (*ZSCAN4*, *MBD3L2*, *TRIM43*), and, for LNA-treated fibers, potential off-targets post-treatment. For fibers treated with LNA#4, RNA sequencing was performed to assess transcriptome-wide efficacy. As a preliminary *in vivo* test, two LNA gapmers (#1 and #4) or saline were intramuscularly injected thrice, once every other day, into the tibialis anterior (TA) muscle of adult *FLExDUX4* mice, an FSHD model expressing human *DUX4*. *DUX4* expression in treated muscle was then evaluated by qPCR.

Results. All designed gapmers significantly knocked down *DUX4* expression *in vitro* by up to ~100% at a 100 nM dose. *ZSCAN4*, *MBD3L2*, and *TRIM43* expression was likewise significantly reduced following treatment. Significant *DUX4* knockdown could also be achieved at a 10 nM LNA or 2'-MOE gapmer dose. Mostly no off-target effects were observed after LNA gapmer treatment; one off-target effect was found at the 100 nM dose, but disappeared at the 10 nM dose. RNA sequencing analysis revealed that LNA#4 treatment reduced the expression of 74 genes activated in FSHD. Finally, a significant reduction in *DUX4* expression was observed in the TAs of *FLExDUX4* mice treated with LNA#1 or LNA#4.

Conclusions. Treatment with our designed gapmers was capable of significantly reducing *DUX4* expression *in vitro* and, in the case of our LNA gapmers, *in vivo*. Further evaluation of treatment effect, e.g. on muscle cell fusion and apoptosis, will be conducted to confirm efficacy at the phenotype level.

Funded By: WCHRI Graduate Studentship; CIHR; University of Alberta, FSH Society, Friends of Garrett Cumming Research Fund, HM Toupin Neurological Science Research Fund

Abstract #: 199
Presenter: Min Ku Kang
Supervisor: Oana Caluseriu
Title: Solving a genetic mystery of a novel immune disorder in the NF-κB pathway
Authors: Min Ku Kang, Allison Lewis
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Title: Solving a genetic mystery of a novel immune disorder in the NF-κB pathway

Introduction

Severe combined immunodeficiencies (SCID) are a group of genetic disorders marked by complex clinical presentations and high mortality. We have characterized a new human immunodeficiency disorder in a consanguineous First Nation family from Northern Alberta in which comprehensive clinical tests have failed to pinpoint a cause. Combining advanced next generation sequencing techniques, we identified a candidate gene, a crucial molecule activating the NF-κB pathway. Upon stimulation, NF-κB pathway is impaired in the patient fibroblasts compared to controls, as we have already observed that patient derived fibroblast cells have decreased NF-κB nuclear translocation and failure in upregulation of target genes that are crucial for immune function. However, a clear link between these defects and the candidate gene mutation hasn't been made. Thus, this study aimed to bring further evidence that the mutation in the candidate gene is the culprit behind the defective NF-κB pathway in our patient.

Methods

To further support pathogenicity, we performed a rescue experiment by transient transfection introducing the wildtype version of the candidate gene into our patient cells. Next, we used quantitative real time PCR to check if NF-κB pathway target gene up-regulation is restored back to normal in patient cells and compared these results with NF-kB up-regulation on patient and control fibroblasts.

Results

We found that after introducing the wildtype version of our candidate gene into the patient cells, the target genes of the pathway involved in immunity (A20, IκBα and IL8) were up-regulated significantly higher than before stimulation compared with other controls.

Conclusion

We conclude that the candidate gene mutation is the underlying cause behind our patient's unknown SCID. Our research provides further evidence for how the candidate mutation is contributing to the pathogenesis of this novel human disorder expanding the growing list of SCIDs and allowing for timely diagnosis and clinical intervention for affected patients in this inbred population.

Funded By: Northern Alberta Clinical Trials and Research Centre (NACTRC) Summer Student Award

Abstract #: 200
Presenter: Sabrina Fox
Supervisor: Rachel Wevrick
Title: Using CRISPR iSTOP to study the role of MAGEL2 in arthrogryposis
Authors: Sabrina Fox, Matthea Sanderson
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

Arthrogryposis is a congenital disease that is characterized by a permanent shortening of the muscles and joints, thereby limiting joint rotation and movement. This restricted movement can significantly lower the quality of life of affected infants. Arthrogryposis can be caused by maternal viral infections, abnormal changes to the amniotic fluid, and genetic mutations. Some mutations can cause a protein to become too active, making it toxic to the cell. This toxicity may cause more problems than having none of the protein at all. MAGEL2 is an example of a gene that, when truncated, produces a protein that potentially exerts a toxic effect on developing joints, bones, and muscles. By studying how this potentially toxic MAGEL2 protein interacts with other proteins in the cell, we can better understand how it causes the shortening of muscles and tendons during embryonic development that leads to arthrogryposis.

Methods

To introduce potentially toxic mutations into MAGEL2, a variation of CRISPR gene-editing was used. This variation is known as CRISPR iSTOP. This gene-editing method allows us to introduce premature stop codons into MAGEL2 at very specific points, thereby creating truncated proteins similar to those seen in patients with arthrogryposis. This gene-editing technique was used to introduce mutations into MAGEL2 in several stable cell lines. The resulting interactions between MAGEL2 and other proteins will be analyzed using several biochemical and cellular assays. This, in turn, may allow us to understand how truncations in the MAGEL2 protein cause arthrogryposis at a cellular level.

Results

Over the course of this project the templates for four CRISPR guide RNAs were successfully cloned into a corresponding CRISPR backbone. The resulting CRISPR plasmid was transfected into stable cell lines and the transfected population of cells are currently being selected to create a homogenous population of cells that carry a mutation in MAGEL2.

Conclusions

CRISPR iSTOP is a novel technique that allows us to increase our understanding of how mutations in MAGEL2 cause arthrogryposis. More specifically, we can use this molecular tool to better understand the effect of truncated MAGEL2 on protein-protein interactions in the cell. This understanding could potentially be used to produce therapies for arthrogryposis that specifically target MAGEL2 or other proteins that it interacts with, therefore increasing the quality of life of infants affected by arthrogryposis.

SF was supported by a WCHRI summer studentship. This study was funded by the Foundation for Prader-Willi Research.

Funded By: WCHRI Summer Studentship; Foundation for Prader-Willi Research

Abstract #: 201
Presenter: Morgan Sosniuk
Supervisor: Lori West
Title: Pediatric possibilities: potent antigen presenting cells improve the established mixed lymphocyte reaction
Authors: Morgan Sosniuk, Anne Halpin, Esmé Dijke, David Fung, Patricia Campbell, Lori West
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

INTRODUCTION: Despite immunosuppression, transplant rejection, such as antibody mediated rejection may occur. Our goal is to explore T cell responses in pediatric heart transplant recipients who develop donor-specific antibody to human leukocyte antigen (HLA). We used mixed lymphocyte reaction (MLR) to measure reactivity between recipient and donor cells. MLR experiments and flow cytometry phenotyping were previously performed using peripheral blood mononuclear cells and irradiated splenocytes. However, despite T cell proliferation responses in all positive controls, including PHA and CD3/CD28 beads, proliferation to donor cells was undetectable. Only small samples are available from pediatric patients thus assay modifications may be required. Dendritic cells are the most efficient antigen presenting cell (APC) making them a promising alternative to enhance the reactivity of this established MLR assay. To optimize MLR reactivity we compared use of donor splenocyte *vs* donor monocyte-derived dendritic cell (moDC) stimulators. T cell responses were measured by proliferation dye combined with the Duraclone Basic flow cytometry panel to label the lymphocyte populations; this panel was previously validated for use with low cell numbers.

METHODS: Monocytes were isolated from donor splenocytes and moDCs were generated by incubation with GM-CSF and IL-4. 5.0-10^4 responder and irradiated donor cells were incubated at 37°C for 7 days. T cell responses were measured by proliferation dye combined with the Duraclone Basic flow cytometry panel to label the lymphocyte populations. Proliferation controls included PHA, CD3/CD28, and CD2/3/28 tetramer. Proliferation was compared between moDC or splenocyte stimulation.

RESULTS: Clear CD4 and CD8 T cell proliferation was detected to positive controls in all experiments; however, the moDC were more potent stimulators of T cell proliferation than splenocytes alone. This dry, pre-formulated panel provided standardized staining of the MLR responses and differentiation of cell populations.

CONCLUSION: The moDC offer a clear advantage in these MLR experiments. A challenge in pediatric research is small sample volumes. With small volumes, only a limited number of viable responder cells are available for use in MLR. Using more potent APCs may be required in the setting of low responder cell numbers. We will use donor moDC as the MLR stimulator cells combined with the Duraclone panel for future experiments carried out with our selected patients and controls.

Funded By: AIHS Summer Studentship

Abstract #: 202
Presenter: Jordana Fersovich
Supervisor: Lori West
Title: Tolerance to A-antigen after treatment of infant or adult mice with MHC-matched A-expressing blood cells
Authors: Jordana Fersovich, Bruce Motyka, Brendon Lamarche, Morgan Sosniuk, Kesheng Tao, Jean Pearcey, Christopher Cairo, Todd Lowary, Lori West
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: ABO-incompatible heart transplantation (ABOi HTx) is safe during infancy and allows increased donor access. Post-ABOi HTx B cell tolerance develops to donor blood group antigen(s) by mechanisms not fully defined. We developed A-transgenic mice (A-Tg) that express A-antigen on vascular endothelium and erythrocytes and demonstrated A-antigen specific tolerance induced by HTx into 4 wk-old, MHC-identical, wild-type (WT) mice. Herein, we explored intentional tolerance induction in infant and adult WT mice using A-Tg blood cells (BC).

Methods: WT BALB/c mice were injected ip (weeklyx3) with intact A-Tg BALB/c BC (±40Gy irradiated), beginning at 7 days (neonates) or 5 months of age (adults). Two weeks after treatment, all mice were injected ip (weeklyx5) with human A-erythrocytes (A-sensitized) in an attempt to elicit anti-A antibody (Ab) production. Serum anti-A and 3rd-party (non-A anti-human) Ab were assessed by hemagglutination assay.

Results: In response to A-sensitization, high levels of anti-A Ab were produced in untreated mice (median titre 1:256, n=11). In contrast, anti-A remained undetectable (≤1:2) in A-sensitized mice treated as neonates with irradiated (n=5) or non-irradiated A-Tg BC (n=6) ($p<0.0001$). Treatment of adult mice with A-Tg BC resulted in reduced anti-A production in response to A-sensitization compared with untreated mice ($p<0.05$). Adult mice with undetectable natural anti-A Ab prior to treatment produced less anti-A (≤1:2 to 1:4, n=5) vs those with pre-existing natural anti-A Ab (1:16 to 1:64, n=5) ($p<0.05$). Mice treated with enriched A-Tg RBC as neonates produced undetectable anti-A Ab (≤1:2, n=4) following A-sensitization, in contrast to those treated with enriched A-Tg PBMCs as neonates (≤1:2048, n=3) ($p<0.0001$). Third-party Ab responses were high for all groups (≥1:128).

Conclusions: Our results suggest that the erythrocyte component of A-Tg blood cells can induce robust A-antigen-specific tolerance in WT mice. Importantly, our findings suggest that tolerance to A-antigen is not limited to the neonatal period but can also be induced in adults, especially in mice without previously detectable natural anti-A Ab. Intentional induction of tolerance to A/B-antigen(s) may allow subsequent ABOi HTx.

Funded By: Alberta Innovates Health Solutions

Abstract #: 203
Presenter: Stephanie Dijk
Supervisor: Eytan Wine
Title: Dietary and microbial interactions in pediatric Inflammatory Bowel Diseases
Authors: Stephanie Dijk, Heather Armstrong, Michael Bording-Jorgensen, Morgan Lawley, Deenaz Zaidi, Matthew Carroll, Hien Huynh, Eytan Wine
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Approximately 25% of inflammatory bowel disease (IBD) cases, including Crohn disease (CD) and ulcerative colitis (UC), are diagnosed in children. These chronic intestinal disorders affect approximately 1 in 150 Canadians and manifest with chronic gastrointestinal inflammation accompanied by altered microbial composition. Dietary changes are relevant in IBD, including the effective pediatric CD therapy exclusive enteral nutrition (EEN), which entails exclusive intake of liquid meal-replacement for 6-8 weeks. As adherence to this treatment can be challenging and costly to families, more accurate identification of patients likely to respond would help limit this treatment to the patients most likely to receive benefit. Establishing reliable biological indicators for this purpose requires a better understanding of IBD pathogenesis. Our studies support the theory that intestinal microorganisms are involved in the development of IBD. We hypothesize these effects may be mediated through an altered intestinal microbiome in response to dietary or bacterial secreted metabolites. Accordingly, we investigated whether these metabolites will vary in response to diet, making previous diet a potential marker of candidates for EEN treatment success.

Methods: Pre-diagnosis food frequency questionnaire (FFQ) data were used to predict EEN outcomes. These are then correlated with intestinal metabolomics to identify potential metabolic pathways linking diet with response to therapy. The effect of these metabolites on bacterial invasion, epithelial barrier integrity, and inflammation are then assessed *in vitro*.

Results: Pilot FFQ analysis correlated intake of simple carbohydrate and processed meat with EEN failure and success, respectively, in pediatric CD patients. Previous metabolomics analysis of intestinal washes showed increased succinate content in IBD patient washes compared to controls. Exposure to IBD patient intestinal washes increased invasion of Enterohemorrhagic *Escherichia coli* into Caco-2 cells in gentamicin protection assays, suggesting that the IBD gut environment made bacteria more invasive. Indeed, metabolomics analysis revealed a correlation between succinate and bacterial invasiveness. These results were replicated *in vitro* with gentamicin protection assays showing that succinate increased invasion of *E. coli* into HT29 cells. Bacteria isolated from IBD patients have also shown increased invasion compared to identical species isolated from non-IBD controls. Invasion of these bacteria was increased in the presence of succinate.

Conclusions: We have shown that previous diet predicts response to therapy and that bacterial invasion is impacted by metabolites. Understanding the interactions between the diet and microbiome in pediatric IBD can guide novel dietary or metabolite-focused therapies and facilitate identification of patients likely to respond to dietary therapies.

Funded By: Crohn's & Colitis Foundation of America

Abstract #: 204
Presenter: Jasmeen Saini
Supervisor: Silvia Pagliardini
Title: Effect of etonogestrel on ventilation in adult female rats
Authors: Jasmeen Saini, Landon DeHoog
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction:

It is well known that progesterone acts both centrally and peripherally as a respiratory stimulant, as women who are in the luteal phase of their menstrual cycle or during pregnancy experience periods of hyperventilation, and post-menopausal women display an increased frequency of sleep disordered breathing compared to pre-menopausal women.

Congenital central hypoventilation syndrome (CCHS) is a disorder caused by a genetic mutation of the transcription factor PHOX2B, which is essential for neural development of several classes of neurons in the brainstem. CCHS is associated with the inability to maintain proper ventilation and blood gas levels during sleep. There is no effective cure for the disease and the only option for treatment is mechanical ventilation or diaphragm pacing. Respiratory stimulants have proven ineffective, with the exception of a recent report indicating a 2-3 fold increase in the ventilatory response to hypercapnia in female CCHS patients that implemented desogestrel, a potent progestin and contraceptive, into their daily regimen.

In this study we hypothesized that etonogestrel (ETO; the active metabolite of desogestrel) stimulates progesterone receptor expressing neurons to increase ventilation.

Methods:

Adult female rats were instrumented with implants to chronically deliver ETO (or sham rats) over a four-week period. An additional group of rats was also treated with 17bestradiol (E2) to increase progesterone receptor expression in presence of ETO or sham rats. Rats were then tested weekly in whole-body plethysmographs to determine changes in respiratory parameters (frequency, tidal volume, and minute ventilation) during baseline conditions (normoxia) and respiratory challenges (hypercapnia and hypoxia). At the end of the treatment period, response to hypoxia and hypercapnia was also tested under isofluorane anesthesia.

Results:

Our results indicate that ETO does not affect the hypercapnic or hypoxic ventilatory response in freely behaving healthy female rats. However, ETO or E2 induce potentiation in the second phase of the hypoxic ventilatory response under isofluorane anesthesia.

Conclusion:

The use of Nexplanon rods to chronically deliver ETO over a four-week period did not result in any change in ventilatory responses in freely behaving rats. However, under isoflurane anesthesia we observed a potentiation in the secondary phase of the hypoxic ventilatory response.

Funded By: CIHR; Merck's Investigator Initiated Program

Abstract #: 205
Presenter: Jashan Saini
Supervisor: Silvia Pagliardini
Title: Afferent brainstem projections to the conditional expiratory oscillator, the parafacial respiratory group (pFRG) in adult male rats.
Authors: Vivian Biancardi, Jashan Saini, Silvia Pagliardini
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction

The ventral respiratory column in the brainstem is divided into subregions which are known to be involved with each phase of breathing. The parafacial respiratory group (pFRG) contains essential neurocircuitry for expiratory rhythmogenesis, particularly active expiration through the recruitment of abdominal muscles. Active expiration leads to an increase in ventilation and produces a more effective breathing pattern. During restful breathing this region is silent; however, under conditions of elevated respiratory drive such as hypoxia, hypercapnia, and exercise the pFRG is active. Furthermore, work from our laboratory has demonstrated that active expiration is also present during rapid-eye movement sleep (REM) and has been hypothesized to be involved in counteracting breathing irregularities during sleep, a state in which most centrally-associated breathing disorders occur (apnea of prematurity, SIDS, hypoventilation syndromes). The aim of our study was to identify and characterize regions in the brainstem that project to the pFRG and may influence its activity in wakefulness and sleep.

Methods

We unilaterally injected into the pFRG a retrograde virus (300 nL of Herpes Simplex Virus) that expressed a fluorescent reporter (enhanced yellow fluorescent protein) in order to identify neurons projecting to the pFRG. Following a postoperative recovery period to allow the expression of the virus, animals were transcardially perfused and the brains were extracted, cryoprotected and processed for histology and RNAscope (RNA in-situ hybridization). Several markers were used to identify the phenotypes of the labelled neurons.

Results

We provide supporting evidence for projections to the pFRG from the medullary ventral respiratory column which includes the ventral respiratory group, preBötzinger complex, Bötzinger complex, and *nucleus tractus solitarius*, as well as projections from the pedunculopontine tegmentum, laterodosral tegmentum, and the midbrain periaqueductal gray. We have also observed projections from the parvocellular reticular nucleus and the intermediate reticular nucleus.

Conclusions

We conclude that the pFRG receives direct projections from regions involved in respiratory rhythmogenesis and in control of breathing, in addition to regions that control other behavioural or physiological states, such as REM sleep and defence mechanisms. Our results suggest potential targets for manipulation of active expiration across sleep states and in respiratory disorders.

Funded By: WCHRI Innovation Grant; CIHR

Abstract #: 206
Presenter: Tanya Voth
Supervisor: Shannon Scott
Title: SPOR – innovation in pediatric clinical trials initiative: Patient-informed recruitment
Authors: Anne Le, Lisa Knisley, Tanya Voth, Shannon Scott
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Background: Clinical trials are crucial to the development of novel treatments and determining best practices in clinical care. There have been numerous research studies conducted on four common health problems: breathing problems, dehydration, stomach upset, and pain. However, evidence as applied to pediatric populations is limited. The Innovation in Pediatric Clinical Trials Program (PI, T. Klassen; funded by CIHR) aims to improve care in these four domains by developing innovative ways to engage parents and involve them in the research process from conception to dissemination. Identifying parents' information needs and preferences is crucial in order to achieve patient informed recruitment.

Objective: To determine parents' and families' preferred venues of contact and information needs with regards to child health research studies. This information will inform the recruitment strategy used in four separate pediatric clinical trials focusing on breathing problems, dehydration, upset stomach, and pain.

Methods: Parents were contacted via email through our partner organizations' electronic mailing lists, which include: The AB SPOR SUPPORT Unit Patient Engagement panel, TREKK Edmonton and Winnipeg Pediatric Parent Advisory Groups, Manitoba Centre for Healthcare Innovation Patient and Public Advisory Group, and the University of Alberta and Calgary HICCUP database. Each email included the full study information letter along with a link to the survey. Parents answered 29 multiple choice research questions and 7 demographics questions.

Results/Conclusion: 77 parents out of 261 reached responded (29.5%). Results indicate that respondents were very interested in hearing about opportunities to participate in children health research (98.7%), particularly from their physician (88.4%). Parents are also receptive to information from: school and community newsletters (87.1% and 84.5%, respectively), posters at schools or community centres (68.9%) or clinic waiting rooms (85.8%). Parents indicated that they would like to receive updates on studies their child has participated in (96.1%), particularly study progress (79.3%), results (100%), and researchers involved in studies (68.9%). Parents would like to be provided with support to participate in research studies (i.e., travel or child care) (83.2%). 77.9% of parents indicated that their child has participated in a research study and of that proportion, only 28.6% were informed of the study results.

Funded By: WCHRI Partnership resources; CIHR

Abstract #: 207
Presenter: Navjot Singh
Supervisor: Olga Petrovskaya
Title: Methodological and ethical challenges of conducting ethnographic research in Alberta Health Services (AHS) clinical settings
Authors: Navjot Singh, Simran Singh, Olga Petrovskaya
Affiliations: University of Alberta
Research Activity: Children's Health and Well-Being

Introduction: Currently, the AHS is working to create a province-wide Clinical Information System, Connect Care. This project includes the implementation of the electronic patient portal, MyChart, providing patients with online access to their health providers (via secure messaging), test results, medication lists, and appointment self-scheduling. In the Edmonton Zone, a few outpatient clinics and some family practices have piloted MyChart.

Ample research literature, mostly American, reports on various effects that electronic portals have on patient- and health provider experiences and patient outcomes. However, this overwhelmingly-quantitative literature is ill suited to illuminate the mechanisms and contextual factors behind the observed effects and experiences as well as the processes of interaction between humans and health information technologies (HIT). In contrast, ethnographic fieldwork, especially as practiced in the UK tradition, is considered the gold standard for examining the processes surrounding the implementation of HIT in clinical settings and for advising various stakeholders and policy makers on these matters.

However, ethnographic or field studies usually remain poorly understood among medical researchers, funding agencies, and even some Research Ethics Boards. This creates challenges for researchers seeking to conduct ethnographic studies. In addition, the nature of the fieldwork itself generates unique challenges for ethnographers.

Methods: Our multidisciplinary research team, led by a PhD-prepared Registered Nurse and consisting of three physicians (one of whom is an AHS administrator) and a pharmacist, designed an ethnographic study to examine the processes (workflow changes, human-machine interactions) and patient and staff perspectives surrounding the implementation of MyChart patient portal in one of the Stollery outpatient clinics. This research was funded by WCHRI (June 2018).

In this case study, we (the PI and RAs involved in parent recruitment) present our early experience of conducting this study. We reflect on selected methodological and ethical challenges in our fieldwork.

Results: Our primary focus will be on our efforts to satisfy the requirements of research ethics committees. Under this umbrella, we will discuss negotiating entry into the field (clinic); the procedures for obtaining participant informed consent; the logistics of participant recruitment and data collection such as extended periods of time ethnographers spend in the research setting.

Conclusions: We concur with other health care ethnographers that the processes set up to govern and oversee the ethical conduct of research are primarily based on the model of biomedical research. This model has little relevance to and insight into the nature of fieldwork, stifling the potential of ethnographic approach.

Funded By: WCHRI Start-up or Retention Funding

Abstract #: 208
Presenter: Wan Kong Yip
Supervisor: Maya Shumlevitz
Title: Mutation in reovirus mu2 reduce specific infectivity but promote replication and dissemination in tumorigenic cells
Authors: Wan Kong Yip, Maya Shumlevitz
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

The non-pathogenic wild-type serotype 3 mammalian orthoreovirus (Reo-wt) is one of the most evaluated oncolytic virus in clinical trials. We identified a variant (Reo-10M) with a single amino acid change in the mu2 protein that shows improved replication over Reo-wt specific to cancer cells. Our data demonstrates that the mutation in Reo-10M mu2 has both infection-hindering and –promoting effects, with an overall net benefit for replication in cancer cells.

Methods and Results

We used tumorigenic mouse fibroblast (L929) and human non-small cell lung carcinoma (H1299) to investigate the biological functions of Reo-10M mu2. First, we found that despite similar binding to cells and uncoating, Reo-10M established infection in 50% fewer cells relative to Reo-wt as determined by flow cytometric analysis. Mu2 is a polymerase co-factor, and our *in vitro* phosphate release and qRT-PCR assays showed that Reo-10M mu2 was less efficient at hydrolyzing ribonucleotide triphosphates (rNTP) and RNA synthesis, likely explaining the reduced establishment of infection. However, when equivalent Reo-wt or Reo-10M infected cells were analyzed by Western blot analysis and qRT-PCR, Reo-10M accumulated up to 4-fold more viral proteins and 3-fold more viral RNAs relative to the Reo-wt virus. In addition to its role in transcription, mu2 also participates in creation of viral factories; localized areas of virus amplification and progeny assembly. Interestingly, immunoprecipitation of mu2 and Western blot analysis for other viral proteins showed that Reo-10M mu2 associated with uNS and other viral proteins 2-fold more efficiently than wt mu2.

Conclusions

The mu2 mutation in Reo-10M reduces the efficiency of rNTP hydrolysis and RNA synthesis thereby reducing establishment of infection. However, the mutation increases the association of mu2 with factory components, augments levels of virus RNA, proteins and progeny, and ultimately promotes virus replication in cancer cells.

Funded By: CIHR; Alberta Cancer Foundation

Abstract #: 209
Presenter: Kate Greeff
Supervisor: Jonathan Tankel
Title: An alphanumeric paging system: an ongoing quality improvement project
Authors: Kate Greeff, Jennifer Mateshaytis
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

INTRODUCTION: Many tertiary care centers utilize alphanumeric paging systems. According to a review of the literature, the results of switching to a message based paging system have been extremely positive. The process of text-paging sends a message that includes pertinent information to allow the recipient to triage the page appropriately - subsequently improving patient care.

METHODS: Pre-intervention Likert format surveys were distributed to OBGYN residents and L&D RNs, to evaluate the current paging practices at RAH. This included questions assessing perceptions of efficiency, ability to triage, effectiveness of communication and patient safety. The survey responses were anonymous, and collected via REDcap. The alphanumeric paging system was then implemented for a two-month trial period. Nursing staff were educated on how to page using a specific reproducible template which included the location, urgency and context of the page. Post-intervention Likert format surveys were distributed to reassess the perceptions of the paging process, and to solicit feedback on the change. The data was collected and analyzed via REDcap.

Results: Comparison between pre-and post intervention surveys obtained from the Labour and Delivery nurses and residents were resoundingly positive with regards to impact on patient care. Due to positive results, we have expanded the alphanumeric paging system to the OBGYN wards with ongoing data collection. Survery results from RNs demonstrated improved efficiency in communication as well as decreased time taken to respond to patient needs. Residents found that with standard numeric paging there were significant numbers of non-urgent pages that interrupted patient care. The introduction of message-based paging showed an improved ability of residents to triage urgent vs non-urgent pages, reducing these interuptions.

CONCLUSION: Implementation of an alphanumeric paging system for the Royal Alexandra Hospital Labour and Delivery Unit achieved the objective of this quality improvement project by streamlining communication between nurses and residents with the goal of enhancing patient safety. The improvement of resident efficiency, response time to emergent situations and triaging abilities has led to the ongoing implementation of the alphanumeric paging system to the general OBGYN wards, with plans to extend to attending physicans in the future.

Abstract #: 210
Presenter: Kristin Black
Supervisor: Peggy Sagle
Title: Availability of medical education podcasts in Obstetrics and Gynecology: a scoping review
Authors: Kristin Black, Lindsay Drummond, Venu Jain, Sue Ross, Peggy Sagle
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Podcasts are audio recordings that users can access online and are a popular means of knowledge acquisition. Approximately 10 million Canadian adults have listened to a podcast in the past year, with the majority of listeners being 18 – 34 years old. Podcasts have been demonstrated to be an effective learning tool in medical education. The uptake of podcasts is high in many areas of medicine, however there is limited information about podcast use in Obstetrics and Gynecology. The purpose of this review is to determine the availability of medical education podcasts in Obstetrics and Gynecology.

Methods

A comprehensive search of commonly used podcast hosting platforms including iTunes, Stitcher.com, and tunein.com was performed to identify potentially relevant podcasts. Titles and descriptions of those podcasts were initially screened by two independent reviewers, followed by a second round of screening applying full inclusion and exclusion criteria. Data were extracted and summarized using Microsoft Excel.

Results

There were 65 potentially relevant podcasts identified from initial searches, 18 of which were included in the review. Podcasts were included if they were English language, publicly available, intended for a medical audience, and the content was primarily in Obstetrics and Gynecology. The majority were produced in the United States, followed by Australia, Ireland, United Kingdom, and India; none were produced in Canada. Three of the included podcasts were produced by medical journals. Seven of the podcasts identified as being teaching podcasts directed at medical students or residents, and covered general topics in Obstetrics and Gynecology. Of these seven, only two were producing new content.

Conclusion

This scoping review is the first to demonstrate an absence of medical education podcasts with content for Canadian medical students and residents in Obstetrics and Gynecology. Future directions for this project include development of an educational podcast in Obstetrics and Gynecology and testing its effectiveness as a learning tool.

Funded By: WCHRI Support services

Abstract #: 211
Presenter: Allison Edwards
Supervisor: Jeanelle Sabourin
Title: Does a structured formative feedback system improve learner perception of the obstetrics and gynecology clerkship? An observational study.
Authors: Allison Edwards, Jeanelle Sabourin
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Medical students are more likely to pursue specialty training in fields they perceived positively during their training. This can be influenced by their satisfaction with feedback during a rotation. We investigated whether a structured formative feedback system would improve learner perception of the Obstetrics and Gynecology clerkship.

Methods: This observational cohort study included medical students from the Class of 2017 (control cohort) and 2018 (intervention cohort). A formative feedback system was implemented during Obstetrics and Gynecology rotations for the Class of 2018. It consisted of a set of electronic feedback forms asking for strengths and requirements for improvement in the student's assessment of a patient with a particular presenting complaint. Students were invited to complete a survey about their overall rotation experience during their final year of training using Likert Scales. The primary outcome was the proportion of students who reported a positive experience during their rotation. Chi-squared analysis was used to compare the proportion of positive responses between each group.

Results: 190/286 (66.4%) students responded to the survey. 65/87 (74.7%) and 72/103 (70.6%) students reported a positive experience on their rotation (good, very good or excellent) in the intervention and control cohorts, respectively (p=0.5). The system helped 50 (57.5%) to obtain constructive feedback and 38 (43.6%) to interact with the clinical team. Only 27 (31%) felt it positively influenced the rotation and 40 (45.9%) felt it helped them to understand course objectives.

Conclusion: Obstetrics and Gynecology is a unique rotation for medical students and their experience can highly influence their aspirations for training. In this study, learner perception of the rotation did not change with implementation of a structured formative feedback system. In the future, these systems likely need to ensure that students receive specific and actionable feedback.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant

Abstract #: 212
Presenter: Helen Yang
Supervisor: Sue Ross
Title: Does cost influence the choice of disposable vs. reusable instruments? Survey of obstetrician/gynecologists.
Authors: Helen Yang, Sue Ross, Val Capstick
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

Use of disposable instruments in laparoscopic procedures has been cited as a major contributing factor driving up the cost of instrumentation and hospital expenditures. A "cost awareness" campaign was therefore undertaken at a tertiary hospital from 2015 to 2016 to raise awareness about costs of disposable versus reusable instruments in laparoscopic procedures. To date, there is limited understanding of factors aside from cost awareness that may influence surgeons' selection of surgical instruments that leads to cost reduction. In order to answer this question, we surveyed the obstetrician/gynecologists (Ob/Gyns) to explore their perception and attitudes toward disposable vs. reusable instruments and determine what influences their choice of instruments.

Methods

A 4-part questionnaire was designed for this study, which included questions about participant demographics, participants' perceived advantages and disadvantages of disposable and reusable instruments and qualities influencing his/her decision to use a particular instrument. In 2015 and 2017, all full-time university-associated Ob/Gyns were mailed a cover letter, the questionnaire and coffee card ($5) with postage-paid return envelope. Responses (with unique ID) from Ob/Gyns who perform laparoscopic procedures were entered into a password-protected REDCap database on a secure server. All statistical analyses were performed by SAS 9.4.

Results

35/42 eligible Ob/Gyns (85%) completed questionnaires before and after the intervention, with median 10 years in practice. The majority had undertaken MIS training, mainly during residency (80%) and conferences (71%). Before the intervention, the three most important qualities influencing their decision to use a particular instrument were safety (66%), effectiveness (57%) and personal experience (49%), and after the intervention were effectiveness (57%), safety (57%) and ease of use (46%). Device cost was ranked sixth (26%) before and seventh (17%) after.

Conclusion

Given the current economy, operative costs are constantly under review. Knowledge about Ob/Gyns' attitudes provides information to design more effective awareness campaigns to encourage use of less costly instruments. To change practice, a campaign increasing Ob/Gyns' exposure to cheaper but safe and effective instruments may help to increase uptake and potentially lead to cost reduction. Cost awareness alone is unlikely to change practice.

Funded By: WCHRI Resident/Clinical Fellow Trainee Research Grant; Trainee Travel Grant

Abstract #: 213
Presenter: Ginevra Mills
Supervisor: Jeanelle Sabourin
Title: Experiences of parenting in residency among female residents in Alberta
Authors: Ginevra Mills, Jeanealle Sabourin, Erica Dance
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction

The proportion of women in medicine continues to increase. More than half of female trainees will have their first child during residency training and the conflicting demands of parenting on residents' time adds stress to an already stressful period. Little research has been done to characterize or improve the pregnancy and motherhood experiences of female residents in training.

Methods

A qualitative, anonymous online survey was distributed by the PGME offices at the Universities of Alberta and Calgary and made available between November 2017 and January 2018. All female residents who identified as having pregnancies or children in residency were eligible to respond.

Results

There were 118 completed surveys, equally divided between both Universities. Respondents included non-surgical (55.1%), surgical (21.2%), and family medicine (23.7%) trainees. The majority of respondents felt that their program directors, physician staff, and resident colleagues were neutral or supportive of their family planning choices in residency and most who took a maternity leave felt that it was adequate. However, almost half chose not to continue breastfeeding upon returning to work because of lack of lactation support and/or conflicts with clinical duties. Over half reported witnessing or personally experiencing colleagues making derogatory comments about female trainees deciding to become pregnant or have children during residency. The parenting experience in residency of our female trainees made 42% of them strongly reconsider their career choices in their chosen field.

Conclusions

The survey responses yielded significant insight into the experiences of female resident mothers in Alberta. While most were neutral or positive in nature, a number of recurrent challenges are identified. The results suggest that there is a need for a more supportive, non-judgmental, and breastfeeding friendly model for residency training in Alberta.

Funded By: WCHRI Support services

Abstract #: 214
Presenter: Ivy Porter
Supervisor: David Brindley
Title: Determining if Dexamethasone can improve outcomes from radiotherapy for breast cancer
Authors: Ivy Porter, Guanmin Meng, David Brindley
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Background: Breast cancer is the most frequent cancer in women and it affects one in eight Canadian women. It is a major cause of mortality since eight in ten women die within five years when the cancer has spread to other organs (metastasis). To prevent this, breast tumours are normally removed surgically (lumpectomy). This is followed by sixteen daily doses of radiation to the remaining breast to kill remaining cancer cells and prevent their spread. However, this treatment is not always effective. Our group discovered that each dose of radiation damages the breast tissue, which stimulates autotaxin secretion. Autotaxin produces lysophosphatidate, which activates an inflammatory cycle involving the release of inflammatory cytokines. These cytokines in turn increase further autotaxin secretion. This inflammatory reaction protects breast cancer cells from further destruction by the radiotherapy. In addition, inflammation increases scarring (fibrosis) in the breast, which causes distress, discomfort and adverse physical changes in about one in five women following radiotherapy. Such scarring requires further medical treatment and cosmetic reconstruction.

The purpose of our project is to learn how to decrease inflammation caused by radiotherapy. We used a compound called dexamethasone, which is a glucocorticoid commonly used clinically to treat inflammation. However, dexamethasone has not yet been used to improve the effectiveness of radiotherapy and prevent subsequent scarring.

Hypothesis: That dexamethasone will decrease autotaxin secretion during radiation therapy to the whole breast and therefore decrease inflammation. This will improve the efficacy of further fractions of radiation in destroying remaining cancer cells and decrease the likelihood of developing clinically significant scarring.

Methods: Use cultured human adipose tissue (fat) to determine the effects of dexamethasone in the radiation-induced production of inflammatory mediators and autotaxin.

Outcomes: Dexamethasone decreased autotaxin secretion compared to the non-treated group. Dexamethasone also significantly decreased the radiation-induced autotaxin secretion. The cytokine and chemokine analysis showed a significant decrease in the secretion of IL-1RA, IL-9, CCL4, TNFb, VEGFA, IL-18 and ENA-78 in the radiation plus dexamethasone group compared to radiation alone.

Significance: The next step will be to continue preclinical studies in mice to see if dexamethasone decreases radiation-induced inflammation in the breast fat pad, as well as, the consequent fibrotic changes. If these predictions were to be correct, it would justify a clinical trial to determine if treating breast cancer patients with dexamethasone during radiotherapy could decrease tumor recurrence and scarring of breast tissue.

Funded By: WCHRI Summer Studentship; Alberta Innovates

Abstract #: 215
Presenter: Emily Harvey
Supervisor: Gordon Chan
Title: Loss of Wee1 and Myt1 activity results in centromere fragmentation
Authors: Emily Harvey, Cody Lewis
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction/Objectives:

Regulation of the cell cycle is critical for cell survival. The Cdk1/cyclin B complex is required for entry into mitosis. Cdk1/cyclin B is regulated by Wee1 and Myt1, which inactivate Cdk1/cyclin B through phosphorylation. Wee1 inhibition results in ectopic activation of Cdk1/cyclin B. This aberrant activation in cancer results in premature and prolonged mitosis. This prolonged mitosis can result in DNA damage at the centromere (centromere fragmentation) and cell death. However, some cancer cells exhibit resistance to Wee1 inhibition. This resistance may be caused by Myt1, another regulator of Cdk1/cyclin B.

Methods/Approach:

Using knockdown of Myt1 (siRNA) both alone and in combination with Wee1 inhibition, mitotic phenotypes and cell death were monitored. This was done using western blots to determine the protein level of Myt1 in relation to Wee1 inhibitor resistance and Cdk1 phosphorylation. Immunofluorescent analysis and karyotyping were used to examine the mitotic phenotype, DNA damage, cell structure and cell death. Overexpression of fluorescently tagged Myt1 was examined as well, for localization and overexpression phenotype.

Results/Findings:

Western blots show that high levels of Myt1 protein correlate with a resistance to the Wee1 inhibitor. Immunofluorescence shows that knockdown of Myt1 in combination with Wee1 inhibition causes centromeres to become disassociated from the DNA. Using karyotyping, high levels of chromosome breakage can be seen in the combination treatment. This phenomenon, called centromere fragmentation is a result of premature and prolonged mitosis. This combination treatment also shows an increase in cell death, greater than Myt1 knockdown or Wee1 inhibition alone.

Conclusions:

Knockdown of Myt1 in combination with Wee1 inhibition increases centromere fragmentation. This centromere fragmentation is associated with higher levels of cell death. Native Myt1 expression levels play a role in the sensitivity to Wee1 inhibitors, and Myt1 represents a viable combination target to increase efficacy of Wee1 inhibitors and other checkpoint regulators.

Funded By: NSERC USRA

Abstract #: 216
Presenter: Caitlin Coulombe
Supervisor: Lawrence Le
Title: Investigating imaging modalities available in oral health: A review study
Authors: Caitlin Coulombe, Kim-Cuong T. Nguyen, Paul W. Major, Lawrence H. Le
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction

In order to maintain oral health, it is important for the clinicians to be able to adequately visualize the internal structures. The periodontium, which includes the gingiva and structures supporting the tooth, is a good indicator of overall oral health. There are currently a number of emerging imaging modalities which have the potential to image the internal dento-periodontal structures. Each of these technologies has advantages and limitations. Some of the technologies are limited to in-vitro studies. Currently, the clinical standards are radiography and cone-beam computed tomography. However, the latter modality involves a high level of ionizing radiation. There is a need to explore non-ionizing radiation modality to improve patient care, especially in the population of children and adolescents. The purpose of this study is to examine through the literature the imaging modalities available and study their efficacy.

Method

To conduct this review study, several databases were searched to find the required articles. The databases used include PubMed, MEDLINE, IEEE Xplore, as well as Google Scholar which was used to find additional papers. There were no limitations placed on the searches. The primary search terms used were: periodontium, oral health, mouth, and imaging. These primary terms were used with one or more of the following secondary terms: intraoral x-ray, extraoral x-ray, radiography, computed tomography (CT), cone beam computed tomography (CBCT), tuned aperture computed tomography (TACT), optical coherence tomography (OCT), photoacoustic imaging, laser ultrasound, ultrasound. The results from the database searches were then analyzed to determine what they contributed to the review study and if they provide enough relevant information to be included.

Results

A total of 94 articles were selected using the databases listed above even though the search was not exhaustive. These articles were used to compare the applications, advantages, and limitations of the modalities in question.

Conclusion

A review of the literature available in oral imaging provides a more accurate understanding of the modalities used in clinical situations as well as those which are being tested for potential clinical use. A review study provides the opportunity to summarize the applications, advantages, and limitations of each of the potential modalities. Increasing the information available about these modalities can assist in the development of a better, safer, and more cost-effective clinical diagnostic modality without compromising patient care.

Abstract #: 217
Presenter: Vaishali Sharma
Supervisor: Susan Armijo-Olivo
Title: Effectiveness of exercise therapy on decreasing pain in women with TMD: A pilot randomized-controlled trial
Authors: Vaishali Sharma, Musa Tashfeen, Paula Ospina Lopez, Zenah Gheblawi, Francisca Claveria-Gonzalez, Monika Hartleb
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction:

Musculoskeletal chronic pain disorders, including temporomandibular disorders (TMDs) are prevalent in women. TMD affects the masticatory muscles, the temporomandibular joint, and related structures. A promising treatment for improving TMD has been exercise therapy. Preliminary studies showed that treatment directed to the neck may benefit people with TMDs. However, to the best of our knowledge, no previous study has tested the effectiveness of exercises directed to the neck in isolation to individuals with TMDs. The primary aim of our study is to investigate the effectiveness of exercise therapy on pain intensity when compared with a placebo group in women experiencing chronic TMD. The effectiveness of exercise therapy on jaw functional limitation and performance of the neck flexor muscles was also investigated.

Methods:

Our study was a triple blind, two-armed parallel group and placebo controlled pilot RCT. Women with chronic TMD were randomly assigned to receive neck motor control exercises, or a turned-off innocuous transcutaneous electrical nerve stimulation (i.e. placebo). Both groups received 12 sessions of treatment in 8 weeks. Pain intensity was measured by a Visual Analogue Scale (VAS). The performance of neck flexor muscles was measured through the Craniocervical Flexion Test (CCFT) and the maximal neck flexor contraction. Finally, jaw functional limitation, was measured using the jaw functional scale. Outcomes were measured at baseline, at 8 weeks (post treatment) and 4 months after treatment completion.

Results:

Currently,11 participants have participated in our study; 7 individuals received the placebo arm and 4 individuals received the neck motor control training using visual feedback. These are only preliminary results. Changes pre-post treatment on current pain intensity indicated that subjects receiving neck exercises reduced their pain about 1.9 cm on the VAS; considered a clinically meaningful change. Participants in the placebo group only had a change of 0.8 cm. After exercise training, participants in the intervention group improved 12.5 points on the CCFT, 16 Newtons in the maximal neck strength, and 23 points in the jaw functional limitation. Contrarily, the placebo group demonstrated a decreased neck muscular performance with -20 points on the CCFT and barely no improvement on the maximal neck strength.

Conclusions:

Our preliminary results are promising and encourage further investigation using a larger sample of women experiencing chronic jaw pain. Our findings will help develop treatment strategies for subjects with TMD, as well as providing further insight about possible treatment options for similar musculoskeletal chronic pain disorders.

Funded By: Dentistry Chair's Excellence Fund, School of Dentistry, University of Alberta

Abstract #: 218
Presenter: Alexa Budd
Supervisor: Susan Armijo-Olivo
Title: Understanding pain modulation and brain plasticity after exercise in chronic temporomandibular disorders: A pilot randomized-controlled trial
Authors: Alexa Budd, Susan Armijo-Olivo, Jacqueline Cummine
Affiliations: University of Alberta
Research Activity: Lifelong Women's Health

Introduction: Evidence from brain imaging techniques has shown that individuals with TMDs show alterations in the thalamus, the primary somatosensory cortex, the anterior and mid-cingulate cortices, and the insula. Alterations in both structure (i.e., changes in diffusion, and grey/white matter) and function (changes in blood-oxygenation-level dependent [BOLD] response) provide converging evidence that implicates these regions in TMDs. However, the extent to which these regions, and connectivity among them, are modulated as a function of treatment (e.g., motor control exercise) has yet to be established.

Therefore, our research question is as follows: **What is the impact of exercise therapy on brain networks (measured with resting state fMRI)?** We hypothesize that people with TMDs receiving exercise therapy will have significant changes in connectivity within networks comprised of the following regions: the thalamus, the primary somatosensory cortex, the anterior and mid-cingulate cortices, and the insula. Networks of interest include the Default Mode Network (DMN) and the Sensorimotor Network (SMN). We anticipate decreased connectivity between the thalamus, the insula, and the anterior cingulate after treatment when compared to a placebo group.

Methods: This was a triple-blind, two-armed parallel group, placebo-controlled pilot RCT. Women with chronic TMD were randomly assigned to receive neck motor control exercises, or a turned-off innocuous transcutaneous electrical nerve stimulation (i.e. placebo). Both groups received 12 sessions of treatment in an eight-week period. The main outcome for this analysis is connection strength (i.e., relationship between BOLD signal across brain regions).

Results: Two subjects underwent MRI analysis before and after treatment for our pilot study. MRI images showed that both participants demonstrate comparable connectivity for the DMN and the SMN at baseline. At two-month follow-up, there was minimal change in the DMN for both participants, but a notable change in the SMN. While statistical analysis across time or participants is not feasible for only two participants, the pilot data presented here demonstrates several important competencies with respect to the outlined proposal: 1) feasibility of pre-post treatment plan, 2) feasibility of the data analysis (i.e., isolating networks of interest), 3) consistency in network representations across the two-month time period (within subjects), and 4) consistency in network representation across the two participants (between subjects).

Conclusions: Our work is underway and these are preliminary results. They highlight the feasibility of the methodology and provide insights into the effects of exercise on brain plasticity in TMD patients.

Funded By: Dentistry Chair's Excellence Fund, School of Dentistry, University of Alberta

Abstract #: 219
Presenter: Elizabeth Garcia
Supervisor: Jerome Yager, Sujata Persad
Title: In vitro study of Sulforaphane in oxygen & glucose deprived brain cells
Authors: Elizabeth Garcia, Zeenat Ladak, Edward Armstrong, Jenny Yoon, Jerome Y. Yager, Sujata Persad
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction:

Perinatal brain injury is responsible for a spectrum of mental and physical disabilities, characterized by cerebral palsy. Therapeutic options for the predisposed and injured newborn are limited. Thus, finding effective and preventative therapeutics to protect the fetal brain in utero is vital. Sulforaphane (SFN), the active ingredient of broccoli sprouts, that has shown promise for the injured brain of the newborn and fetus. This work consists of a platform of cell cultures of the major cellular constituents of the brain involved or targeted by injury (Neurons and Astroglia) due to placental insufficiency. Our objective is to evaluate, at the molecular level, the protective effect of SFN on these cellular constituents exposed to oxygen and glucose deprivation (OGD). OGD simulates *in vitro,* the *in vivo* ischemic condition. Our primary hypothesis is that SFN will prevent injury in neuronal cell cultures exposed to OGD.

Methodology:

We developed a rodent newborn cell culture model of primary cortical neurons/astrocytes, which were exposed to OGD insult and 24 hours of recovery with complete media. The effect(s) of OGD were then evaluated in the presence/absence of SFN at different doses to measure the efficacy of SFN in limiting ischemic injury. The purity of the cell cultures was evaluated by Western blot and immunofluorescence (IF) of cell-specific markers, for neurons: NSE (neuron specific enolase), for astrocytes: GFAP (glial fibrillary acidic protein), and for glia: CD68 (cluster of differentiation 68). Cell death was determined by cell viability analysis using IF/high content analysis and cytotoxicity using the calorimetric MTT method.

Results:

We have successfully established our primary cortical neuronal and astroglial cell cultures. We determined the LD50 (duration of OGD required for 50% cell death) as 2 hours for neurons ($p<0.001$) and 4 hours for astrocytes ($p<0.002$). With their LD50 established, the dose of the protective effect of SFN on the primary neurons was 2.5uM ($p<0.0001$), and for astrocytes was 5uM ($p<0.0001$), compared to their respective controls. One Way ANOVA analysis was used for all statistical analysis.

Conclusions:

Our preliminary results indicate that cell death was significantly reduced in neurons and astrocytes treated with SFN. The findings of our studies will provide a platform for future testing of natural health products such as broccoli sprouts containing SFN in the prevention of perinatal brain injury. This study will inform the development of innovative novel therapies to move forward to clinical trials.

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Abstract #: 220
Presenter: Aiden Cottrell-Callbeck
Supervisor: Dr. Denise Hemmings
Title: Increased autotaxin activity in first trimester of women who develop preeclampsia
Authors: Aiden Cottrell-Callbeck, Dr. David Brindley, Dr. Denise Hemmings
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

Introduction - Gestational diabetes (GDM) and preeclampsia (PE) complicate between 1-14% and 2-8% of pregnancies worldwide each year, respectively. Potential biomarkers for PE and GDM include inflammatory factors, but the prognostic value remains inconclusive. Autotaxin (ATX) is a secreted enzyme that produces the inflammatory lipid, lysophosphatidic acid (LPA). LPA decreases the levels ofadiponectin, a protective hormone released from both placenta and adipose tissue during pregnancy and increases the levels of sphingosine 1-phosphate (S1P), a similar lipid with inflammatory effects. The longitudinal relationship among ATX/LPA, adiponectin and S1P in normal pregnancies or those complicated by GDM and PE is not known. In this study, we focused on assessing ATX. Serum ATX concentration, but not enzymatic activity, is reported to increase during normal pregnancy but is even higher in PE at term. However, whether ATX activity reflects this increase in concentration throughout normal pregnancies or if ATX activity in 1st trimester can predict later development of PE or GDM are not known. We hypothesizethat ATX activity will increase throughout normal pregnancy but will be abnormally increased in early gestation of women who develop PE or GDM.

Methods - Plasma samples from a cohort of pregnant women in the Alberta Pregnancy Outcomes and Nutrition (APrON) Study were collected in 1st, 2nd and 3rd trimesters and postpartum. ATX activity was measured using a choline release assay. Differences in plasma ATX activity in women with hypertension prior to 20wks gestation (n=133), hypertension/PE after 20wks gestation (n=18), GDM (n=78) or normal pregnancies (n=259) at each time point were examined by one-way ANOVA.

Results - In normal pregnancy and GDM, plasma ATX activity increased significantly in each trimester to a maximum in 3rd trimester and then decreased to 1st trimester levels postpartum. In PE, plasma ATX activity was increased in 1st trimester and at postpartum compared to controls and GDM ($p<0.05$).

Discussion - Our work indicates that plasma ATX activity in 1st trimester could be prognostic for women at risk of PE. Importantly, we also established a healthy reference range for ATX activity in plasma from a large cohort of normal pregnant women. In contrast to our hypothesis, plasma ATX activity in women with GDM does not differ from that in normal pregnancy. We will now measure LPA, S1P and adiponectin in these same samples, assess confounders and determine whether the combined results provide a stronger prognostic value than ATX alone.

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Abstract #: 221
Presenter: David Jay
Supervisor: Jerome Yager
Title: The effects of intrauterine growth restriction and broccoli sprout supplementation on serotonin and dopamine concentrations through ELISA
Authors: David Jay, Edward Armstrong, Elizabeth Garcia, Jerome Yager
Affiliations: University of Alberta
Research Activity: Maternal and Infant Healthy Development

INTRODUCTION/OBJECTIVE: Intrauterine growth restriction (IUGR) is a form of placental insufficiency (PI) that generates chronic hypoxia in fetuses. IUGR is a risk factor for the development of cerebral palsy (CP) through its inherent induction of perinatal brain injury. We have previously shown that this model causes neurological deficits that are prevented with broccoli sprout (BrSp) consumption. However, there is very little neuropathology to account for these changes in behavior. In this study, we aim to determine if consumption of IUGR induced behavioral changes are due to changes in neurotransmitter receptors like dopamine (DA) and serotonin (5-HT), and if so if these changes are reversed by BrSp treatment.

METHODS: Pregnant Long-Evans rats underwent IUGR and Sham surgery on gestational day (GD) 20 of a 23-day gestation. Dams allocated to receive supplementation were treated with 200 mg/day of dried BrSp from GD15 until postnatal day (PD) 21. The control group dams were fed Chow in the same fashion. Brain samples taken from the rats' cortex, striatum, and the hippocampus were collected on postnatal day 35 and were extracted and homogenized. Protein determinations were done for each sample via BCA protein assay. After normalizing the protein we measured the DA and 5-HT concentrations by Enzyme-Linked Immunosorbent Assay (ELISA). We then used a Univariate ANOVA in SPSS to determine significance in our treatments.

RESULTS: The ELISA measurements revealed that BrSp significantly increased the cortex membrane 5-HT levels of female pups ($p = <0.05$). In addition, the implemented IUGR surgery increased the hippocampus DA concentration of male pups ($p = <0.05$) in the Chow group, but not the BrSp group. Suggesting that BrSp had a protective effect on the DA levels in the hippocampus of male pups. No other receptor concentrations were significantly affected by the diet treatment or surgery. However, preliminary data shows that IUGR surgical procedure increases the DA concentrations in relation to the control (Sham) groups in the Striatal and Cortical regions of male pups. Finally, trends indicate that males may be more susceptible than females to neurotransmitter imbalances caused by IUGR.

CONCLUSIONS: IUGR does cause changes in neurotransmitter receptors and these changes can be affected by BrSp consumption. These findings suggest that BrSp dietary supplementation during pregnancy is a novel, safe and efficacious preventive strategy in the challenge of treating cerebral palsy and developmental disabilities.

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Notes

DISCLAIMER:
While the abstracts have been slightly modified for consistency, each abstract has been predominantly printed exactly as originally submitted.

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