women & children's health research institute

2015 Research Day Abstract Book

The Power of Partnership

University of Alberta

Alberta Health Services

Stollery Children's Hospital Foundation

Lois Hole Hospital for Women

Acknowledgements

Thank you

The Women and Children's Health Research Institute (WCHRI) is a partnership between the University of Alberta and Alberta Health Services and is generously supported by the Stollery Children's Hospital Foundation and donors to the Lois Hole Hospital for Women.

The University of Alberta and the Faculty of Medicine & Dentistry

UNIVERSITY OF ALBERTA

UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Department of Pediatrics

The University of Alberta strives to create and support an environment of research excellence across the university to fuel knowledge advancement, discovery and innovation, all of which contribute significantly to society provincially, nationally and globally. Through the continued support of the U of A and the Faculty of Medicine & Dentistry (FoMD), WCHRI is able to house its research support and administrative staff. FoMD also partially funds WCHRI's operating expenses, without which the institute would not be able to manage its grants programs and research support initiatives.

Alberta Health Services

Alberta Health Services

Alberta Health Services has been a strong and active supporter since WCHRI's inception. Innovative clinical research goes hand-in-hand with providing the best evidence-based patient care for patients in Alberta. AHS has identified "incenting research and innovation of the highest value to Albertans" as one of its top strategic priorities. WCHRI is pleased to be working as a valued research partner with AHS in advancing this priority.

The Stollery Children's Hospital Foundation

STOLLERY CHILDREN'S HOSPITAL FOUNDATION

STOLLERY CHILDREN'S HOSPITAL

The Stollery Children's Hospital Foundation (SCHF) is dedicated to raising funds to build the Stollery Children's Hospital into the best children's health-care delivery, research and teaching institution in the world. The foundation recognizes the tremendous impact that research has on disease prevention, treatment and improved health outcomes for children. Over the ten-year period of May 2006 to April 2016, SCHF committed more than $30 million to support WCHRI, which represents the contributions of thousands of individual donors.

The Royal Alexandra Hospital Foundation

LOIS HOLE HOSPITAL FOR WOMEN

Royal Alexandra HOSPITAL FOUNDATION

The Royal Alexandra Hospital Foundation (RAHF) inspires community support for the Royal Alexandra Hospital and its medical centres of excellence. This includes the Lois Hole Hospital for Women, where donor support brings advanced technologies, facility enhancements and exciting new opportunities for research in women's health. Donor support for this research is provided to the Women and Children's Health Research Institute and totals $11 million over a ten-year period from May 2006 to April 2016.

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Abstract #: 1
Presenter: Caroline Richard
Supervisor: Catherine Field
Title: Feeding a diet enriched in docosahexaenoic acid to lactating dams changes the tolerance response to egg protein in suckled pups
Authors: Caroline Richard, Erin Lewis, Susan Goruk, Catherine Field
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: An important T cell mediated process that occurs early in life is the development of oral tolerance (OT), referring to the ability to distinguish between harmful and harmless antigens delivered via the oral route. Food allergies are believed to be the result of a failure to develop OT to a dietary antigen. Althoughit is well established that long chain polyunsaturated fatty acids (LCPUFA) modulate T cell function, no study has yet documented the effect of feeding a docosahexaenoic acid (DHA) rich diet during the suckling period on the development of this important immune response. The objective of this study was to determine the effect of feeding a maternal diet supplemented with DHA during the suckling period when an OT treatment is induced on the development of the immune system and OT in offspring.

Methods: Sprague-Dawley dams were randomized to one of the two nutritionally adequate experimental diets 24-48h prior to parturition: control diet (N=12, 0% DHA) or high DHA diet (N=8, 0.9% DHA of total fatty acids). Diets were fed to dams *ad libitum* throughout the suckling period and matched for macronutrient, micronutrient and fatty acid content differing only in the composition of omega-3. At 14-days pups from each dam were randomly assigned for 5 d to an oral challenge: placebo (sucrose) or ovalbumin (OVA). At 3 weeks, immune cell phenotypes and cytokine production by mitogens- (Concanavalin A (ConA), lipopolysaccharide (LPS)) or OVA-stimulated splenocytes were measured by direct immunofluorescence assay and ELISA, respectively.

Results: Regardless of the OT treatment, feeding a high DHA diet led to a higher production of IFN-γ by splenocytes stimulated with ConA and a higher production of IL-6, IL-10 and TNF-α after LPS stimulation (all $P<0.05$). After OVA stimulation, splenocytes from suckled pups fed the high DHA diet produced significantly more IL-10 and less TGF-β versus the control diet (both $P<0.02$). The OT treatment with OVA resulted in a lower production of IL-6 by LPS-stimulated splenocytes and led to a higher proportion of cytotoxic T cells expressing CD28 and total cells expressing CD27 (all $P<0.02$).

Conclusion: Our results suggest that feeding a maternal diet enriched in DHA during the suckling period improved the ability of splenocytes to respond *ex vivo* to mitogens and changes the tolerance response to a dietary antigen.

Funded By: Natural Sciences and Engineering Research Council of Canada

Abstract #: 2
Presenter: Sarah Lee
Supervisor: Noreen Willows
Title: Protecting and coping: Exploring the experience of food insecurity among postsecondary students with children
Authors: Sarah Lee, Anna Farmer, Geoff Ball, Noreen Willows
Affiliations: University of Alberta
Research Activity: Women's Health : Nutrition
Investigation Type: Qualitative Research

Introduction

Food insecurity is the limited or uncertain availability of nutritionally adequate and safe foods or limited or uncertain ability to acquire acceptable foods in socially acceptable ways. The condition is associated with adverse nutritional and health outcomes. The Campus Food Bank (CFB) Society at the University of Alberta provides students with food hampers containing a 4-day supply of non-perishable foods, and if available, perishable items. About one-fifth of students requesting hampers have children living with them. The purpose of this qualitative descriptive study was to explore the experience of food insecurity among a sample of postsecondary students with children (PSSC) who received emergency food hampers during the 2013-2014 academic year.

Methods

Participants were recruited purposively at the CFB. Semi-structured face-to-face interviews were digitally recorded and manually transcribed. Transcripts underwent conventional content analysis permitting codes and categories to be drawn from the data using participants' words.

Results

Nine PSSC (n=4 women, n=5 men) were interviewed. Two primary themes emerged from the data: protecting and coping. PSSC **protected** their children from food insecurity by eating lower quality foods and preferentially giving foods of higher nutritional quality to their children. PSSC did not feel the food provided in the CFB food hampers was nutritionally adequate to meet their children's needs. To overcome this perceived shortcoming, PSSC opted to serve their children store-bought food if they could afford to do so, while they consumed the food hamper items. One participant mentioned that their children were concerned that some foods in the hampers were bad to eat because they were past their expiry date. PSSC **coped** with food insecurity using a variety of strategies in addition to accessing the CFB. These strategies included borrowing money, lowering food quality, and accessing emergency food resources from the municipal food bank. Some of the participants noted a feeling of shame about their coping strategies but felt that they were necessary to meet their food needs.

Conclusion

Some postsecondary students with children may be at risk of nutritional inadequacies due to financial crises that lead to food insecurity. PSSC might jeopardize their own well-being as a result of consuming lower quality foods and going hungry to protect their children from nutritional inadequacy and hunger. Increasing financial resources, enhancing nutrition education and developing food assistance programs and policies for PSSC might reduce food insecurity among this group, thereby aiding in the protection of their children.

Funded By:

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Abstract #: 3
Presenter: David Lim
Supervisor: Justine Turner
Title: EXOGENOUS Glucagon-like Peptide-2 Therapy Improves Parenteral Nutrition Associated Liver Disease by Altering Bile Acid Metabolism.
Authors: David Lim, Paul Wales, Si Mi, Jason Yap, Jonathan Curtis, Diana Mager, Catherine Field, Pamela Wizzard, David Bigam, Justine Turner
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Quantitative Research

Introduction: Parenteral nutrition-associated liver disease (PNALD) is a significant cause of morbidity and mortality for infants with intestinal failure (IF). While glucagon-like peptide-2 (GLP-2) is being advanced as therapy for IF, the effect of GLP-2 treatment on PNALD is unknown.

Objective: To investigate the effect of exogenous GLP-2 administration on hepatic function in a preclinical model of neonatal PNALD.

Methods: Neonatal piglets (age 2-6 days) underwent jugular venous catheterization to receive iso-nitrogenous, iso-caloric total parenteral nutrition (PN). Piglets were randomized to either GLP-2 (11 nmol/kg/day) treatment (n=7) or saline control (n=8). A group of age-matched sow-reared piglets (n=8) was studied to represent normal physiology. After 17 days, piglets underwent terminal laparotomy and bile flow was measured. Liver specimens were analyzed histologically and with immunoperoxidase staining. The relative gene expression of enzymes involved in bile acid synthesis, regulation and transport was measured in liver by qRT-PCR. Bile acid composition in bile was determined using tandem mass spectrometry. Data are analyzed using one-way ANOVA or Kruskal-Wallis analysis of variance.

Results: Both PN-fed groups developed cholestasis relative to sow-reared piglets, as evidenced by a decrease in bile flow and increased serum total bilirubin. GLP-2 treatment ameliorated bile flow (1.35 µl/g vs. 0.73 µl/g; $p = 0.02$) and total bilirubin (38.0 µmol/L vs. 78.5 µmol/L; $p = 0.008$) compared to saline control. Histologically, GLP-2 treatment was associated with decreased hepatocyte pigmentation (a marker of cholestatic injury) compared to saline control. There was no difference in serum C-reactive protein levels or Ki67 and cleaved caspase-3 staining. GLP-2 increased FXR ($p<0.001$) and CYP7A1 expression ($p=0.03$). The paradoxical increase in CYP7A1 may be a consequence of increased LXRα ($p<0.01$) and LRH-1 ($p=0.003$) expression. GLP-2 treatment increased the expression of bile acid export genes: canalicular MRP2 ($p=0.002$) and basolateral MRP3 ($p=0.037$) over saline control. GLP-2 treatment was associated with decreased concentrations of taurohyocholic acid and conjugates of toxic lithocholic acid ($p<0.01$).

Conclusions: Exogenous GLP-2 treatment in a preclinical model of neonatal PNALD improves cholestasis. Mechanistically, this finding may be mediated by alterations in the hepatic expression of genes involved in bile acid metabolism. The transcriptomic results indicate the mechanisms at the transcriptional level acting to decrease bile acid synthesis and increase bile acid export. Furthermore, GLP-2 therapy is associated with a less toxic bile profile. Our findings support a novel beneficial role for GLP-2 therapy in PNALD.

Funded By: Graduate Studentship

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Abstract #: 4
Presenter: Arnaldo Perez
Supervisor: Geoff Ball
Title: Why do parents discontinue health services for managing pediatric obesity?
Authors: Jasmine Dhaliwal, Arnaldo Perez, Nicholas Holt, Rebecca Gokiert, Jean-Pierre Chanoine, Katherine Morrison, Laurent Legault, Arya Sharma, Geoff Ball
Affiliations: University of Alberta
Research Activity: Children's Health
Investigation Type:

Purpose: To explore parents' reasons for discontinuing tertiary-level care for pediatric weight management.

Methods: Participants included parents with children (10 to 17 years old; body mass index ≥85th percentile)whowere referred for pediatric weight management. Parents were recruited from three sites (Vancouver, BC; Edmonton, AB; Hamilton, ON) and were eligible if their children attended ≥1 clinical appointment and subsequently discontinued care. Data were collected using semi-structured individual interviews that were digitally recorded, transcribed, and analyzed using the categorical aggregation method.

Results Parents (n=29) of children [mean age: 14.7±1.8 years; mean BMI percentile: 98.9±1.6; sex: 17 males (58.6%)] were primarily female (n=26; 89.7%), Caucasian (n=22; 75.9%), and had a university degree (n=23; 79.3%). Reasons for discontinuing care were grouped into three categories: *(i)* family factors (*e.g.,* perceived lack of progress; lack of family support; children's decision to drop out), *(ii)* logistical factors (*e.g.,* monetary costs; distance; scheduling), and *(iii)* health services factors (*e.g.,* discharged from care; unmet care expectations).

Conclusions: Family, logistical, and health services factors all influenced parents' decision to discontinue care for pediatric weight management. Clinicians might be able to enhance retention by discussing families' expectations for their care at presentation and tailoring subsequent services to help meet those expectations.

Funded By: Graduate Studentship

Abstract #: 5
Presenter: Deenaz Zaidi
Supervisor: Eytan Wine
Title: Quantitative analysis of capillary flow rate in the duodenum of pediatric inflammatory bowel diseases.
Authors: Deenaz Zaidi, Lucas Churchill, Hien Huyn, Matthew Carroll, Eytan Wine
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: Inflammatory Bowel Diseases (IBD), including Crohn disease (CD) and ulcerative colitis (UC), are increasing in children. While involving mainly the gastrointestinal tract, these diseases also manifest extraintestinal affects, indicative of broad-spread systemic involvement, not mere localized pathogenesis. While disease site typically differs between CD (small and large bowel) and UC (colorectal), duodenal involvement has also been reported in children with IBD. We have previously found increased epithelial gaps in uninflamed duodenum in UC patients using probe-based confocal laser endomicroscopy (pCLE), an optical imaging technique that enables visualization of the mucosal surface and microvascular circulation. Vascular changes are well-characterized features of IBD. Thus, assessing structural and circulatory changes in the duodenum even in the absence of inflammation is critical to better understand early stages of disease pathogenesis. We hypothesized that changes in duodenal microvascular circulation (as detected by pCLE) are associated with pediatric IBD and contribute to pathogenesis. Our objective was to assess changes in capillary flow rate in duodenal images obtained using pCLE during endoscopy in children with IBD and correlate them with disease activity and inflammatory markers.

Methods: pCLE was used to analyze capillary blood flow rate in the duodenum of IBD and non-IBD patients. Fifty six patients (33 non-IBD, 14 CD and 9 UC), between the ages of 3-18 were included in the study. Confocal imaging of the duodenum was conducted during endoscopy. Images of villi with visible blood vessels were captured as video sequences. Capillary flow rate was calculated frame-by-frame as:

Distance travelled by blood cells divided by the duration of the sequence = capillary flow rate (µm/ms)

Results: Duodenal capillary flow rate, blindly measured by 2 reviewers, was significantly higher in UC patients (0.78 ± 0.07) as compared to non-IBD (0.59 ± 0.03) and CD patients (0.65 ± 0.04) µm/ms. There was no correlation between PUCAI, PCDAI, serum CRP, ESR, and capillary flow rate in CD and UC patients.

Conclusions: The study shows, for the first time, increased capillary blood flow in the duodenum of UC patients in the absence of localized inflammation, that was unrelated to inflammatory markers and disease activity, suggesting that vascular changes may not result from inflammation alone. Thus, early vascular changes can be assessed with pCLE during endoscopy. Further analysis at the molecular level will provide important insight into early vascular changes and their role in disease pathogenesis.

Funded By: Graduate Studentship

Abstract #: 6
Presenter: Leticia Pereira
Supervisor: Carla Prado
Title: Comparison of resting energy expenditure predictive equations in exclusively breastfeeding women
Authors: Leticia Pereira, Sarah Elliott, Linda McCargar, Emmanuel Guigard , Rhonda Bell, Carla Prado, ENRICH Research Team
Affiliations: University of Alberta
Research Activity: Women's Health : Nutrition
Investigation Type: Quantitative Research

Introduction: Assessment of energy needs in postpartum women is crucial for weight management in clinical practice. Resting energy expenditure (REE) is the largest component of total energy expenditure, representing the minimal energy required for function of vital organs. REE is measured by indirect calorimetry, and the whole body calorimetry unit is the gold standard method to measure it. However, due to the impracticality of measuring REE in all women, predictive equations are usually used to estimate REE and subsequently, energy requirements. This study compared measured versus estimated REE to determine the accuracy of predictive equations in exclusively breastfeeding women.

Methods: Thirty exclusively breastfeeding women, 31.7 ± 3.8 years, were studied at 3.2 ± 0.2 months postpartum. REE was measured by indirect calorimetry in a whole body calorimetry unit. Women underwent evaluation after at least a 10-hour fast, and after being minimally physical active in the 24 hours prior to the test. Measured REE was compared with predictive equations commonly used to estimate REE in clinical practice: Harris and Benedict (1919), Cunninghan (1980), Bernstein (1983), Schofield (1985), Owen (1986), and Mifflin-St Jeor (1990) equations. These equations use participant's demographic and anthropometric, or when required, body composition data (measured by dual-energy X-ray absorptiometry) to estimate REE. Paired t-tests and the Bland and Altman method was used to compare measured and predicted REE. Bias was calculated as the mean difference between measured and predicted REE.

Results: Average body mass index was 25.9 ± 4.7 kg/m^2 and measured REE was 1442 ± 177 kcal/day. The Harris and Benedict equation overestimated REE (1504± 156 kcal/day, p< 0.0001; bias: 63 kcal, 95% limits of agreement = -102 to 227 kcal); and Owen (1313 ± 111 kcal/day, p< 0.0001; bias: -129 kcal, 95% limits of agreement = -320 to 62 kcal) and Bernstein equations (1218 ± 116 kcal/day, p< 0.0001; bias: -224 kcal, 95% CI: -409 to -38 kcal) underestimated REE values. The Mifflin-St Jeor was the most accurate equation (1445 ± 180 kcal/day; bias: 2.8 kcal, 95% limits of agreement = -169 to 175 kcal), and Bernstein was the least accurate equation.

Conclusion: The Mifflin-St Jeor equation most accurately estimated REE in exclusively breastfeeding women with a bias value lower than 3kcal. This equation can be easily used in clinical practice, and it can assist clinicians in determining energy requirements, and hence weight management in the postpartum period.

Funded By: Trainee Travel Grant

women & children's health research institute

Abstract #: 7
Presenter: Barbara S.E. Verstraeten
Supervisor: David M. Olson
Title: Stress and Interleukin-1β (IL-1β) adversely influence maternal and offspring outcomes in rat pregnancy: a two-hit hypothesis.
Authors: Barbara S.E. Verstraeten, J. Keiko McCreary, Ashlee Matkin, Hans Verstraelen, Gerlinde A.S. Metz, David M. Olson
Affiliations: University of Alberta
Research Activity: Maternal Research : Pre-term Birth
Investigation Type: Quantitative Research

Introduction: Preterm birth (PTB) is the leading cause of perinatal morbidity and mortality worldwide. It was suggested that perinatal programming by stress increases the PTB and low birth weight risk. We previously showed that ancestral stress in rats influences PTB risk as well as maternal and newborn outcomes. Here, we propose a "two-hit" hypothesis whereby prenatal events cumulatively influence pregnancy outcomes, while neither hit apart does.

Methods: Pregnant Long-Evans rats were exposed to external stress and an immune challenge (IL-1β injection). Rats were separated into four groups: no stress/saline (NS/S); stress/saline (S/S); no stress/IL-1β (NS/IL-1β); stress/IL-1β (S/IL-1β). Stress was forced swimming (5min/day) and restraint (20min/day) on gestational day (GD) 12-18. IL-1β injection (5μg/kg/day, i.p.) was administered from GD17-delivery. Blood samples were acquired before breeding, GD18 and lactation day (LD)1. Gestational length, maternal blood glucose and gestational weight (baseline-GD11-18-21), offspring weight on postnatal day (P)1-P30 and eye opening (P14) were recorded. One-way, repeated measures and two-way ANOVA or non-parametric equivalents were performed with post-hoc testing. Significance was set at $p \leq 0.05$.

Results: 70% of stress/IL-1b dams had an adverse pregnancy outcome (early/late delivery, miscarriage, dystocia) vs. one adverse event in each of the other groups. Maternal glucose levels did not differ significantly between the four groups nor did maternal weight at different time points, while maternal weight gain between GD11 and GD18 varied significantly in absolute and percent gain ($p<0.001$). S/IL-1β mothers gained significantly less weight than otherwise treated animals ($p<0.001$ – $p<0.01$). Prenatal stress and IL-1β also impacted pup weight with an effect of both treatment and sex ($p \leq 0.05$ and $p<0.001$). The treatment effect was visible at P1 ($p<0.001$) with S/IL-1β offspring weighing less than other pups (±0.7g, $p<0.001$). Females were always lighter than males ($p <0.05$ –
$p<0.001$). Male offspring weights were also significantly different between groups at P30 ($p<0.05$). Eye opening on P14 varied significantly as well ($p<0.001$), with S/S having more opening than NS/S ($p<0.001$) and S/IL-1β ($p<0.05$).

Conclusions: Stress/IL-1β led to more adverse pregnancy events in this two-hit model. Maternal weight gain and newborn weights were lower in the group that received both stressors. Offspring from externally stressed mothers had both eyes open earlier than any other group. External and immune stressors appear to act cumulatively on some maternal and offspring outcomes, while having no or a mitigating effect on others. Models combining multiple hits and ancestral stress might better explain the link between stress and preterm birth.

Funded By: PhD Fellowship - Research Fund Flanders, CIHR

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Abstract #: 8
Presenter: Mais Aljunaidy
Supervisor: Sandra Davidge
Title: Effect of Maternal Antioxidant MitoQ on Cardiomyocyte Development in a Rat Model of Intrauterine Growth Restriction (IUGR)
Authors: Mais Aljunaidy, Jude Morton, Raven Kirschenman, Vanessa Vuong, Tom Phillips, Patrick Case, Christy-Lynn Cooke, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal Research : Fetal Origins of Adult Disease
Investigation Type: Quantitative Research

Introduction: Intrauterine growth restriction (IUGR), a pregnancy complication in which a fetus does not reach its genetic growth potential, is a leading cause of fetal morbidity and mortality and is linked to cardiovascular disease later in life. Maternal hypoxia can lead to placental oxidative stress, which is associated with IUGR and abnormal fetal cardiomyocyte development. Mitochondria are a primary source of oxidative stress in the placenta. We hypothesized that maternal treatment with MitoQ, a mitochondrial antioxidant, prevents IUGR and abnormal development of fetal cardiomyocytes.

Methods: Pregnant rats were randomly divided into two groups, and injected with either MitoQ loaded nanoparticles (125 μM) or saline via tail vein on gestational day (GD) 15 (nanoparticles restrict the treatment to the placenta and prevents its passage to the fetus). Rats were further subdivided into two groups exposed to either hypoxia (11% O_2) or normoxia (21% O_2) from GD 15-21 (term; 22 days). On GD 21, pups were separated into males and females, and

their body, placenta and heart weights were assessed. Placental oxidative stress was assessed by performing DCF (dichlorofluorescein) staining. The length, width, area and binucleated of cardiomyocytes were assessed. A 2-way ANOVA was used for statistical analyses.

Results: Hypoxia led to IUGR in both male and female fetuses. MitoQ treatment prevented IUGR in females only. Relative placental weight (normalized to fetal body weight) was not altered among the groups in either sex. Hypoxia was associated with increased placental oxidative stress which was prevented by MitoQ treatment. In male and female fetuses, relative heart weight was increased in groups exposed to hypoxia and was normalized following MitoQ treatment. In male fetuses, relative cardiomyocyte area (normalized to heart weight) was significantly increased in the hypoxic group (normoxia: 19133 ± 1914 μm2/g vs. hypoxia: 25735 ± 1911 μm /g, $P<0.05$) and MitoQ treatment prevented this (hypoxia + MitoQ: 17103 ± 1932 μm /g). Cardiomyocyte size and area were not affected by hypoxia or by MitoQ treatment in female fetuses. No differences in cardiomyocyte binucleation were observed between the groups in either male or female fetuses.

Conclusion: Maternal hypoxia caused IUGR in male and female fetuses and increased cardiomyocyte hypertrophy in male fetuses. Preventing placental oxidative stress using MitoQ may be a novel approach to improve fetal outcomes, including specific effects on cardiac development.

Funded By: Graduate Studentship

Abstract #: 9
Presenter: Amy Toosi
Supervisor: Dawn Kingston
Title: Increasing awareness about the benefits of a pre-conceptional multivitamin containing folic acid among international migrant women
Authors: Amy Toosi, Dawn Kingston, Kathy Hegadoren
Affiliations: University of Alberta
Research Activity: Maternal Research : Nutrution
Investigation Type: Quantitative Research

Introduction

Strong evidence exists that consumption of a folic acid supplement before and during pregnancy can reduce the risk of neural tube, cardiovascular and limb defects. There are differences in knowledge about benefits of pre-conceptional folic acid supplementation between international migrant (54%) and Canadian- born (82%) women. Research also shows that international migrant women do not access preventative care, but they do access primary health care providers to seek care. We target primary health care providers to increase awareness in this population.

Methods

The aim of this study was to increase awareness for childbearing aged international migrant women of the benefits of pre-conceptional folic acid supplementation.

A randomized control trial pilot was performed in five community health centers to evaluate the effectiveness of an intervention on folic acid awareness for international migrant women aged 18-45. The intervention group received a pamphlet in English and their native language about the benefits of pre- conceptional folic acid supplementation and had a discussion with a healthcare provider.

Results

The majority of the women were 26-30 years old and lived in Canada for 4.5±3.8 years. Women in the intervention group were more likely to know the benefits of folic acid (94%) compared to the control group (41%) χ^2 (1,N=34)=10.89, and to use a folic acid supplement in future pregnancies (100%) compared to the control group (29%) χ^2 (1,N=34)=14.17, p=0.001. The majority (59%) reported that the pamphlet in their native language was more useful than English (18%) and discussion with a health provider (23%).

Conclusion

This intervention proved to be effective in closing the knowledge gap between Canadian-born and international migrant women's awareness of the benefits of pre-concepional folic acid. The usefulness of providing written information to international migrants in their native language rather than a discussion with a healthcare provider, as the main source of information, offers an opportunity for low cost health promotion in a variety of settings. This approach will ensure that international migrants with language barriers receive and understand health information.

Funded By: Trainee Travel Grant

women & children's health research institute

Abstract #: 10
Presenter: Qendresa Beka
Supervisor: Padma Kaul
Title: Impact of gestational diabetes mellitus and maternal mental illness on the development of diabetes, hypertension and cardiovascular disease
Authors: Qendresa Beka, Anamaria Savu, Dawn Kingston, Padma Kaul, Jeffrey Johnson
Affiliations: University of Alberta
Research Activity: Maternal Research : Perinatal Mental Health
Investigation Type: Quantitative Research

Introduction: Gestational diabetes mellitus (GDM) and mental illness have been shown to individually increase the risk of developing chronic disease. However, their combined impact on long-term maternal outcomes has not been previously studied. We examined the individual and combined associations of mental illness and GDM and subsequent chronic disease development in a large population-based cohort.

Methods: The study population was mothers of singleton deliveries in Alberta from April 1999 to March 2010. Data from a provincial perinatal registry were linked to administrative health databases to gather information on maternal characteristics and outcomes. Mothers were categorized into four mutually exclusive groups according to diagnoses during pregnancy: both mental illness and GDM, only mental illness, only GDM, neither mental illness nor GDM. Cox proportional hazards models were used to calculate the relative hazard of developing diabetes, hypertension or cardiovascular disease for each group.

Results: Our population consisted of 240,085 women with a median follow-up of 5.3 years. Compared to women with neither mental illness or GDM (n=205,592), the hazard ratios (95% CI) of developing diabetes, hypertension, and CVD were, respectively, 18.8 (17.0, 20.9), 2.1 (1.9, 2.3), and 1.5(1.1, 2.0)
among women with only GDM (n=24,762); 1.2(1.0, 1.4), 1.2(1.1, 1.2) and 1.3(1.1, 1.5), among women with only mental illness (n=7,735); and 20.7(17.1, 25.0),
2.1(1.7, 2.7), and 2.5(1.4, 4.5) among women with both GDM and mental illness (n=996; *Table 1*).

Conclusion: Women with GDM and mental illness, and especially when they co-occur, during pregnancy have a higher risk of developing chronic disease. Intervention programs targeting both these risk factors may reduce the risk of long-term maternal outcomes.

Table 1

	Adjusted Hazard Ratios		
	Diabetes	Hypertension	Cardiovascular disease
No GDM, no mental illness	1.00	1.00	1.00
Mental illness only	1.2 (1.0, 1.4)	1.2 (1.1, 1.2)	1.3 (1.1, 1.5)
GDM only	18.8 (17.0, 20.9)	2.1 (1.9, 2.3)	1.5 (1.1, 2.0)
Both GDM and mental illness	20.7 (17.1, 25.0)	2.1 (1.7, 2.7)	2.5 (1.4, 4.5)

Funded By:

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Abstract #: 11
Presenter: Sarah Elliott
Supervisor: Rhonda Bell
Title: Gestational weight gain: influence on postpartum weight retention and body composition at 3 months postpartum
Authors: Sarah Elliott, Leticia Pereira, Emmanuel Guigard, Linda McCargar, Rhonda Bell, Carla Prado, ENRICH Study Team
Affiliations: University of Alberta
Research Activity: Women's Health : Nutrition
Investigation Type: Quantitative Research

Introduction: The postpartum and inter-pregnancy periods are critical times when successful weight management is important in reducing the risk of obesity. Excess gestational weight gain (GWG) and storage of fat during pregnancy are potential risk factors for postpartum weight retention and may alter the trajectory of weight loss and body composition change in the postpartum period. The aim of this exploratory analysis was to examine the relationship between excess GWG, weight retention, and regional body composition at 3 months postpartum in women recruited to a longitudinal study about postpartum energy metabolism.

Methods: 51 women aged 32.5 ± 4.1 years reported their pre-pregnancy weight and highest weight during pregnancy. Women were then categorized according to having either met or exceeded Health Canada guidelines for GWG during pregnancy (highest weight in pregnancy minus pre-pregnancy weight). At 3.2 ± 0.2 months postpartum, height and weight were measured; total and regional % body fat (Android: trunk and upper body region and Gynoid: hips, thighs, lower body region) were assessed by Dual Energy X-ray Absorptiometry (DXA). Weight retention was defined as weight at 3 months postpartum minus pre-pregnancy weight. Group differences were computed using student's t-test after determining equality of variance for each variable. Significance was set a $p<0.05$.

Results: Average GWG was 15.2 ± 5.1kg, with 53% of women exceeding GWG guidelines. Women who exceeded GWG guidelines retained more weight than those who met guidelines (6.9 ± 5.6kg vs. 1.7 ± 3.1kg, $p<0.0001$) and had a higher total % body fat (41.1 ± 7.4% vs. 35.7 ± 8.4%, $p=0.01$) and higher Gynoid region % body fat (49.2 ± 6.4% vs. 44.9 ± 6.9%, $p=0.01$). No difference in total Android region % body fat was observed between the two groups (46.4 ± 10.4% vs. 41.9 ± 10.6%, $p=0.07$).

Conclusions: Exceeding GWG was associated with higher postpartum weight retention, higher total % body fat and a higher Gynoid region % body fat at 3 months postpartum. Further investigation into the specific regional (Android and Gynoid compartments) differences in body composition between the two groups is needed. The excess weight and fat stored during pregnancy may influence the course of weight and body composition changes during the postpartum period. Follow up of these women at 9 months postpartum, coupled with detailed information on their dietary intake and energy expenditure will help elucidate this.

Funded By:

women & children's health research institute

Abstract #: 12
Presenter: Cindy Kao
Supervisor: Sandra Davidge
Title: Mechanism of Vascular Dysfunction Due to Circulating Factors in Women with Preeclampsia
Authors: Cindy K. Kao, Jude S. Morton, Anita L. Quoun, Sandra T. Davidge
Affiliations: University of Alberta
Research Activity: Maternal Research : Preeclampsia
Investigation Type: Quantitative Research

INTRODUCTION: Preeclampsia (PE), as defined by new-onset hypertension after 20 weeks of gestation with proteinuria, affects 5-10% of pregnant women worldwide. Circulating factors have been proposed to play a major role in the pathophysiology of endothelial dysfunction observed in PE. However, the mechanism(s) leading to altered vascular reactivity remain unclear. We hypothesize that circulating factors in PE plasma lead to endothelial dysfunction by increasing oxidative stress and reducing nitric oxide and prostaglandin bioavailability.

METHODS: Pregnant rat uterine and mesenteric arteries were harvested and incubated overnight with 3% normotensive (NP) or PE plasma collected from women upon admission to hospital. Responses to methacholine, an endothelium-dependent vasodilator, were obtained using wire myography to assess endothelial function pathways. Vascular superoxide production was measured via dihydroethidium staining and nitric oxide synthase (NOS) expression via Western blots.

RESULTS: PE plasma significantly increased superoxide production and impaired endothelial function in uterine arteries (E_{max} 79.9 ± 5.6% vs. 44.9 ± 6.3%, p = 0.0004), which was restored in the presence of oxidant scavengers or prostaglandin synthesis inhibition. Uterine artery vasodilation was abolished in the presence of pan nitric oxide synthase inhibition in both NP- and PE-treated vessels, but the contribution of nitric oxide to endothelial vasodilation was significantly reduced in PE-exposed vessels ($p < 0.001$). Interestingly, inducible NOS-dependent vasodilation was present only in NP-treated and not in PE-treat arteries. Uterine arteries exposed to PE plasma also exhibit an increased endothelial NOS expression and a decreased inducible NOS expression. PE plasma did not alter endothelial function in mesenteric arteries, suggesting the effect of circulating factors on endothelial function was vascular bed specific.

CONCLUSION: We have shown that circulating factors contribute to endothelial dysfunction via altered oxidative stress and vasodilator pathways, specifically by decreasing nitric oxide availability and increasing prostaglandin synthase dependent vasoconstrictors. This study contributes to the collective understanding of the pathophysiology of PE and we strive to find a potential pharmacological target for its treatment.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 13
Presenter: Amrita Bhattacharjee
Supervisor: Samina Ali
Title: Pre-hospital dexamethasone administration in children with croup: A medical record review
Authors: Amrita Bhattacharjee, Aaron Moodley, Dominic Allain, Eddie Chang, Allison Kabaroff, Kevin Lobay, Samina Ali
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Background: Croup is one of the most common childhood respiratory illnesses, affecting more than 80,000 Canadian children per year. Early dexamethasone administration in croup can reduce admission rates, length of stay (LOS), transfers to the intensive care unit, number of intensive care unit days and number of intubations, frequency of administration of nebulized epinephrine, as well as return visits to the emergency department (ED). Pre-hospital emergency medical services (EMS) paramedic teams in Edmonton now administer dexamethasone to children with croup. The objectives of this study were to (a) assess the clinical impact of pre-hospital administration of dexamethasone to children with croup and (b) compare clinical outcomes of these patients to those who did not receive their first dose of dexamethasone via the EMS providers.

Methods: This study was conducted as a retrospective medical record review that included children between 6 months and 6 years of age who were brought via
EMS to the Stollery Children's Hospital ED with a final ICD-10 diagnosis of croup, between January 1st 2010 and December 31st 2012. Data were collected regarding pre-hospital presentation and management, ED presentation and management, ED LOS and final disposition, and patient demographics.

Results: 188 patients with ED diagnosis of croup were enrolled, 35.1% (n=66) of whom received a pre-hospital diagnosis of croup. The mean age of the participants was 32.96 + 17.18 months. 10.6% of patients (20/188) were given dexamethasone in the pre-hospital setting (i.e. by EMS personnel), while 57/188 patients (30.3%) were given epinephrine nebulizers by EMS. Out of the 66 patients with a pre-hospital diagnosis of croup, 10.6% (n=7) were given dexamethasone by EMS. In the ED, dexamethasone was administered to 88.3% 166/188 patients (166/188) while 29.8% of participants (56/188) received Epinephrine nebs. There was no significant difference in ED LOS stay between those who received pre-hospital dexamethasone (2.6 + 1.6 hours, n=18) and those who did not (3.3 + 2.7 hours, n=159). The number of in-hospital epinephrine doses per patient was significantly influenced by the administration of pre-hospital dexamethasone (p=0.010).

Conclusions: Pre-hospital administration of dexamethasone likely influences the severity and short-term persistence of croup symptoms, as evidenced by less epinephrine use in the ED. Contrary to current EMS guidelines, very few patients with a pre-hospital diagnosis of croup received dexamethasone by EMS personnel. This represents a missed opportunity to administer dexamethasone early and possibly decrease the severity of the patients' disease.

Funded By: Trainee Research Grant

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Abstract #: 14
Presenter: Allison Lewis
Supervisor: Oana Caluseriu
Title: From bench to bedside: a novel mutation in the NF-κB pathway may cause immunodeficiency.
Authors: Allison Lewis, Paulo Nuin, Heather Leonard, Oana Caluseriu
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Quantitative Research

Introduction:

As many as 80,000 Albertans are affected by rare diseases; with the greatest prevalence in children such diseases dramatically impact the lives of both those suffering and the families caring for them. Severe combined immunodeficiency (SCID) represents a group of inherited disorders characterized by immune system impairment due to dysfunctional lymphocytes. Ectodermal dysplasia with immunodeficiency (EDA-ID) is a rare disorder where patients experience abnormalities of the ectodermal structures in addition to immunodeficiency. EDA-ID is most often caused by mutations in the NEMO gene, a critical regulator of the NF-κB pathway.

Methods:

This study focused on finding the cause of a life-threatening immunodeficiency with features of affecting a child of Cree descent born to consanguineous parents from Alberta. Conventional genetic testing for SCID was unable to provide a diagnosis prompting an in-depth investigation for possibly novel genetic causes. We used homozygosity mapping and whole-exome sequencing to narrow down and select regions of interest in the genome, and identify possible candidate genes. *In silico* modelling of common variants was used to prioritize them based on predicted pathogenicity. Sanger sequencing was used to perform segregational studies of high priority variants within the family.

Results:

Homozygosity mapping and whole-exome sequencing data was analyzed according to autosomal recessive inheritance and yielded 4 candidate genes. One variant was strongly predicted to be pathogenic by *in silico* modelling. This gene is a component of the NF-κB pathway and required for NEMO activation, and the mutation is harboured in a domain that is critical for protein structure and function. Familial studies showed that the phenotype segregates with the variant. Future studies to examine the functional implications of this mutation on the protein, and assays in patient derived cells are being planned.

Conclusion:

We are describing a novel phenotype in a family of Cree descent and propose a molecular basis for the disease in a gene not formerly known to cause human disease. Elucidating the causative gene of the disorder in this family has direct implications for the therapeutic choice to treat the deficiency in this child: a bone marrow transplant, as well as on the family as a whole through personalized genetic counselling. Our work provides an example of a translational study using deep sequencing to identify the cause of a genetic disorder with direct implications for the practice of precision genetics.

Funded By: Innovation Grant

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Abstract #: 15
Presenter: Brendon Lamarche
Supervisor: Lori West
Title: ASSESSMENT OF NEONATAL TOLERANCE TO BLOOD GROUP A-ANTIGEN IN A NOVEL MOUSE MODEL OF ABO-INCOMPATIBLE HEART TRANSPLANTATION
Authors: Brendon Lamarche, Katrina Labonte, Szu-I Wang, Jean Pearcey, Kesheng Tao, Michael Mengel, Banu Sis, Bruce Motyka , Lori West
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Transplant
Investigation Type: Quantitative Research

Introduction: ABO-incompatible heart transplantation (ABOi HTx) can be performed safely in infants due to lack of natural anti-A/B antibodies in contrast to adults. Following ABOi HTx, B cell tolerance to donor A/B blood group antigen(s) develops by mechanisms not well understood. We have developed an A- transgenic (A-Tg) mouse model to study mechanisms of tolerance following ABOi HTx. We have previously shown that wild type mice become tolerant to human A-antigen following HTx from an A-expressing donor (MHC syngeneic). The present study investigated whether tolerance can be induced in neonatal WT mice following administration of A-antigen in a form other than a transplant.

Methods: Neonatal WT mice (< 24 hours of age) were injected intravenously with adult splenocytes from A-Tg mice (n=9) or were left untreated (n=8). At 7 weeks of age, all mice were injected intraperitoneally (five doses at weekly intervals) with human A erythrocytes to elicit production of anti-A antibody. Plasma antibodies specific to A-antigen or xenogeneic human erythrocyte antigens were assessed by hemagglutination assay. Neonatal treated (n=4) and untreated (n=3) groups received heterotopic heart transplants from A-Tg donors. Grafts were monitored for function (beating) and assessed for antibody-mediated rejection (AMR) by histology at 14 days post-Tx or when beating ceased. Evidence of chimerism (A-expressing cells in WT mice) was assessed by flow cytometry in some of the treated/non-transplanted mice (n=2) compared to untreated/non-transplanted mice (n=2).

Results: All mice in the untreated group developed anti-A antibodies at high levels (median titre of 1:1024), whereas in the neonatally-treated group only 4/9 mice developed anti-A antibody and this was at a low level (median titre of group was ≤1:2). Anti-human erythrocyte antibodies were detected in both the untreated and treated groups, with median titres of 1:128 and 1:16, respectively. In the untreated group 2 of 3 grafts survived, whereas all grafts in treated mice (4/4) survived to the 14 day endpoint. Immunophenotypic evidence (C4d deposition in capillaries) of AMR was present in one of the surviving grafts in the untreated group and in no grafts in the treated group. Morphologic AMR features are currently being assessed. A-expressing cells were detected within the natural killer (NK) cell population in spleen (5% of NK cells) in treated but not untreated mice.

Conclusion: The inability to elicit abundant production of anti-A antibodies in treated mice suggests that neonatal exposure to A-antigen in the form of A- expressing splenocytes induced A-antigen specific tolerance.

Funded By: Summer Studentship

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Abstract #: 16
Presenter: Szu-I Wang
Supervisor: Lori West
Title: Tracking T Cell Fate after Antithymocyte Globulin (ATG) Immunotherapy in Infant Heart Transplant (HTx) Patients
Authors: Szu-I Wang, Ingrid Larsen, Richard Chinnock, Joyce Rusch, Simon Urschel
Affiliations: University of Alberta
Research Activity: Children's Health
Investigation Type: Quantitative Research

Introduction: Polyclonal T cell depletion with ATG is a common induction therapy in adult and pediatric transplantation. In adults, T cell recovery post-ATG involves homeostatic proliferation of both spared and new thymic emigrant T cells. In infancy, however, HTx patients undergo routine thymectomy, and mechanisms of their immune recovery remain unknown.

Methods: By systematically analyzing T cell profiles at various timepoints, we determined the impact of ATG on immune reconstitution of thymectomized infant HTx pts. Using blood samples from HTx patients (given at < 1 year of age) who received ATG induction, we tracked T cell phenotypes at under 2 years, 2-5 years, and 5-10 years post-transplant. Controls were patients who underwent thymectomy without transplant (Thyx) analyzed at the same timepoints post-surgery and age-matched healthy children (n= minimum 6 for each group at each timepoint). T cells were enriched by magnetic negative selection from cryopreserved peripheral mononuclear cells and phenotyped for presence of memory/naïve markers, recent thymic emigrants (RTE), and regulatory T cells (Treg).

Results: In Thyx patients, the frequency of CD45RA+RO- naïve T cells was moderately decreased while CD45RA-RO+ memory T cells were moderately increased at all three timepoints. In contrast, ATG induction in HTx patients resulted in profound and persistent reduction of naïve cells and rise of memory cells in the CD4+ T cell population. Additionally, while Thyx patients retained approximately 50%of their CD4+ RTE compared to healthy controls at 2 years post-surgery, only 3% remained in HTx patients with ATG induction. The high frequency of memory CD4+ T cells comprised primarily CD62Llo effector memory T cells, while neither Thyx nor HTx with ATG treatment altered the frequency of CD62Lhi central memory T cells relative to healthy controls. ATG-treated HTx pts also acquired a persistent CD45RA+RO+ transitional population in CD8+ T cells.

Conclusion: Interestingly, although ATG has been reported to spare and induce FoxP3+ Tregs in adults, we did not observe significantly increased Treg frequency in infant HTx patients who received ATG induction. To conclude, in contrast to reports in adults, ATG induction did not increase Tregs in infant HTx patients.
Furthermore, ATG induction resulted in a profound and persistent increase in effector memory T cell populations likely due to the lack of thymic output during immune reconstitution.

Funded By: Trainee Travel Grant

Abstract #: 17
Presenter: Shahzma Merani
Supervisor: Shokrollah Elahi
Title: A novel subset of cells modulate and suppress immune responses in newborns
Authors: Shahzma Merani, Wenna Chen, Shokrollah Elahi
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: Neonates are highly susceptible to infections which are often fatal. An infant's immune system cannot control infection or respond to vaccination, which results in vulnerability to infections that are not life threatening to older children or adults. We have recently shown that erythroid precursor cells co- expressing transferring receptor (CD71) and erythroid lineage marker (CD235a or Ter119) are physiologically abundant in newborn mice and human umbilical cord blood (CB). The presence of these cells after birth contributes to the vulnerability of neonates to sever infections, as depletion of these cells enhanced resistance to perinatal pathogens. The mechanisms by which $CD71^+$ $CD235a^+$ cells inhibit the immune responses require further investigation. Specifically, we studied the role of $CD71^+$ $CD235a^+$ cells on T-cell proliferative capacity, T-cell and NK cell cytokine production ability, T-cell activation markers and TLR expressions on antigen presenting cells *in vitro* and *in vivo*.

Methods: CB mononuclear cells (CBMCs) were isolated and functional assays were performed in the presence and/or absence of $CD71^+$ CD235a cells. Similar studies were conducted on splenocytes obtained from newborn mice. Furthermore, *in vivo* depletion of $CD71^+$ $TER119^+$ cells in newborn mice using neutralizing antibody performed to validate our *in vitro* observations.

Results: Our data demonstrated that $CD71^+$ $CD235a^+$ cells play an important role in inhibiting the immune responses in newborns. These cells suppress and modulate T-cell, NK cell and antigen presenting cell responses *in vitro* and *in vivo*.

We believe that presence of these suppressor cells in newborns could interfere with their optimal immune responses, resulting in a potentially poor adaptive immune response to infection and vaccines.

Conclusions: Our current studies will shed light on the mechanisms by which $CD71^+$ $CD235a^+$ modulate and/or suppress immune responses in newborns. Ongoing research in identifying the beneficial and/or detrimental effects of immature erythrocytes on immune responses may serve to enhance protective newborn immune responses to infection and enable better vaccination strategies for the young to be designed.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 18
Presenter: Gonzalo Garcia Guerra
Supervisor:
Title: Pediatric Remote Ischemic Pre-conditioning Prior to Complex Cardiac Surgery: the PREP Pilot Trial
Authors: Gonzalo Garcia Guerra, Ari Joffe, Rob Seal, Irina Dinu, Elham Khodayari , Jonathan Duff, Ernest Phillipos, David Ross, Ivan Rebeyka, Charlene Robertson
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction: Remote Ischemic Pre-Conditioning (RIPC) refers to the finding that a brief ischemia-reperfusion event to a tissue results in subsequent protection from a more severe ischemia-reperfusion event to a different tissue/organ. There are only a few pediatric RIPC studies that show conflicting results. Hence, we conducted a randomized controlled trial (RCT) to determine the effect of early and late RIPC on the acute outcomes of infants after surgery for congenital heart disease (CHD).

Methods: Pilot double blind RCT of RIPC vs. control (sham-RIPC) in infants (<6 weeks old) going for surgery for CHD. Patients were randomly assigned in a 1:1 ratio to receive an RIPC stimulus or control. RIPC was performed at 24-48 hours pre-operatively, and again before CPB. RIPC was done sequentially on each lower limb for 2 cycles. In the control group the cuff was placed underneath the legs. Blinding was achieved by covering the patients' legs during the intervention. Forty-five infants were enrolled the study (23 in the RIPC group and 22 in the control group), patients were analyzed on an intention to treat basis.

Results: Baseline characteristics were similar across both groups. There were no significant differences between the RIPC group and the control group in the highest blood lactate level day 1 post-operative (5.6+3.3 vs. 4.4+3.8 mmol/L; P=0.103), time of blood lactate < 2mmol/L (18.9+17.8 vs. 15.5+12.5 hours; P=0.461) or inotrope scores day 1 post-operative (20.3+23.8 vs. 11.2+6.5 hours; P=0.094). Between groups, there was no significant difference in troponin levels (at 3, 6, 12 and 24 hours), or creatinine levels (day 1 to 5) after surgery. Days on mechanical ventilation (4.6+3.4 vs. 12.8+29.1 days; P=0.193), intensive care length of stay (PCICU LOS) (5.1+2.8 vs. 14.3+32.2 days; P=0.190) and hospital LOS (5.1+2.8 vs. 14.3+32.2 days; P=0.052) were shorter in the RIPC; but these differences were not statistically significant.

Conclusions: In infants who underwent surgery for CHD, our RCT on early and late RIPC did not find any significant difference in acute outcomes. A larger trial may be necessary.

Funded By: Innovation Grant

Abstract #: 19
Presenter: Mohamed Elboraee
Supervisor: Mosarrat Qureshi
Title: The predictive value of hyperlactemia for adverse outcome in infants with moderate to severe hypoxic-ischemic encephalopathy
Authors: Mohamed Elboraee, Ernest Philipos, Leonora Hendson, Amber Reichert, Mosarrat Qureshi
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Mixed Methods

Title: The predictive value of hyperlactemia for adverse outcome in infants with moderate to severe hypoxic-ischemic encephalopathy

Mohamed S. Elboraee[1], Ernest Philipos, Leonora Hendson[1,2,4], Amber Reichert[1,2], Mosarrat J Qureshi[1,3]

[1] University of Alberta, Edmonton AB; [2] Stollery Children's Hospital, Edmonton AB; [3] Royal Alexandra Hospital, Edmonton AB; [4] University of Calgary AB.

Background: Hypoxic-ischemic encephalopathy (HIE) remains one of the most devastating complications in the newborn period. Lactate is invariably produced in the event of hypoxia and poor tissue perfusion. It is not however clear whether early hyperlactemia has a predicting value for the long-term adverse outcomes.

Introduction: Initial highest recorded lactate in the first hour of life and serial measurements of blood lactate have been found to be important predictors of moderate-to-severe newborn encephalopathy in cases of intrapartum asphyxia. We therefore hypothesized that the degree and duration to normalise hyperlactemia in HIE infants can predict neurodevelopmental outcome at 18 months and at 3 years of age.

Objective: To explore the short and long term adverse outcome predicting value of high lactate level in newborns with moderate to severe hypoxic-ischemic encephalopathy after adjustment for confounders.

Methods: A retrospective chart and database (the Neonatal and Infant Follow-up Clinic Database and Neonatal Research Laboratory Database) review for all infants > 35 weeks gestational age (GA) treated in the Northern Alberta Neonatal Program with moderate to severe HIE from January 2006 to December 2012 (excluding babies who were growth restricted on admission or with major congenital anomalies). Two groups were identified: Gp1, term or near term infants with HIE II/III and documented high Lactate levels (>5.0mmol/l); and GP2, those with lactate levels (<5.0mmol/l). Univariate and multivariable regression analyses were used to compare the outcomes of the 2 groups.

Results: Out of 167 infants, 106 infants had initial lactate >5.0mmol/L (63%) and 48 had initial lactate <5.0mmol/L (29%). Data was missing on 13 patients (7%). Disability data was available for 115/167 patients (69%). Thirty two out of the167 patients (19%) died. Initial lactate >5.0mmol/L was statistically significant (p0.0195) for composite outcome of death/disability. In addition, the duration of normalisation of lactate (<2.0mmol/l) data was available for 125/167 (75%) infants and was statistically significant for composite outcome of death or disability (P 0.0011). Table (1)

Table (1) Duration for Normalized Lactate

	Frequency	Percent	Cumulative	Cumulative Percent
<24hr	27	21.60	27	21.60
24hr- 48 hrs	42	33.60	69	55.20
>48 hrs	56	44.80	125	100.00
Missing data for 42 patients				

Conclusions: Most term or near term infants with HIE II/III had initial lactate more than 5 mmol/L, correlating with composite outcome of death/disability. The longer it took to normalize the lactate the poorer the outcome.

Funded By: Trainee Research Grant

Abstract #: 20
Presenter: Lily Lin
Supervisor: Jennifer Conway
Title: Right ventricular strain rate at pre-Glenn assessment may predict prognosis in children with Hypoplastic Left Heart Syndrome
Authors: Lily Lin, Jennifer Conway, Silvia Alvarez, Benjamin Goot, Edythe Tham, Timothy Colen, Shelby Kutty, Nee Khoo
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction

Right ventricle (RV) dysfunction in hypoplastic left heart syndrome (HLHS) predicts mortality. Speckle tracking echo (STE) strain rate (SR) is a validated measure of contractility in HLHS. RV fractional area change (FAC) is a robust measure of RV ejection. We aim to explore the sensitivity (sens) and specificity (spec) of STE deformation and RVFAC on pre stage 2 (S2) echo in predicting death or transplantation (Tx).

Methods

We selected 43 children with "classic" HLHS from prospectively recruited patients with function echo at pre S2. RVFAC and STE longitudinal (long) and circumferential (circ) strain (S) and strain rate (SR) were measured. Data are presented as median, interquartile ranges. Patients were divided into alive (group 1) and died/Tx (group 2) at latest follow up. Wilcoxon's rank sum test was used for comparisons. Receiver operating characteristic analysis was performed with area under curve (AUC), sens, spec, positive (PPV) and negative (NPV) predictive values reported on variables with a $p<0.05$ on univariate analysis.

Results

Fourty-three HLHS patients underwent S2, 6 died and 2 Tx at mean follow up of 4.6 years (0.4 - 9.0). Long S (-16.38 % [-12.04, -16.90] vs -18.44% [-16.09, -20.00]
$p<0.05$); long SR (-0.90 1/s [-0.74, -1.02] vs -1.11 1/s [-1.01, -1.32] $p<0.01$); circ SR (0.801/s [-0.67, -0.92] vs -1.0 1/s [-0.87, -1.22] $p<0.01$) and FAC (34% [28, 39]
vs 41% [38, 47] $p<0.01$) were decreased in group 2 vs group 1 respectively.

AUC for long S 0.73, $p=0.02$; long SR 0.81, $p<0.01$; circ SR 0.83, $p<0.01$ and FAC 0.83,$p<0.01$. Arbitrary cut offs at 75% sens were selected for long SR (-0.97 1/s) and circ SR (-0.86 1/s). FAC cutoff of 35% was used, as it is a recognized lower limit. FAC < 35% has sens 50%, spec 94%, PPV 67%, NPV 89% for detection of death/Tx. With the addition of long or circ SR, the detection sens and NPV were improved; if long SR >-0.97/circ SR >-0.86 or FAC < 35% were present, sens 88%/88%, spec 83%/74%, PPV 54%/44%, NPV 97%/96% respectively.

Conclusion

Abnormal RV FAC in HLHS is highly specific for short to medium term death/Tx post S2. The addition of STE long or circ SR significantly increased test sensitivity and improved NPV. The combined assessment of RV ejection and contractility may provide useful prognostication of HLHS at pre S2 assessment.

Funded By:

Abstract #: 21
Presenter: Silvia Alvarez
Supervisor: Nee Khoo
Title: Left Ventricle Strain Rate in Children Demonstrates Heart Rate Dependence and a Force--
Authors: Silvia Alvarez, Mohammed Alhabden, Michal Kantoch, Joseph Atallah, Timothy Colen, Edythe Tham, Nee Khoo
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Qualitative Research

Background

In adult pigs and human studies, strain rate (SR) is a valid and reproducible marker of contractility. It is also heart rate (HR) independent, hence lacks force- frequency relationship (FFR). Isovolumic acceleration (IVA) is a proven non-invasive load-independent measure of LV contractility used in research settings. This study sought to assess SR behavior during tachycardia and inotropic stimulation in children, compared to IVA.

Methods

Twenty-four patients (median age, 13.9; range 7.8 - 22.5 years) with no structural or functional heart abnormalities were evaluated after a radiofrequency ablation procedure. Echocardiogram was performed at baseline, during atrial pacing and isoprenaline infusion to achieve 130% of baseline HR. Speckle tracking global LV longitudinal SR and tissue Doppler septal IVA were measured. Relationships between HR, SR and IVA were assessed. Percent (%) change and absolute differences between SR and IVA at baseline, pacing and isoprenaline were evaluated. Data are reported as median and interquartile ranges.

Results

SR and IVA showed a moderate correlation with HR at baseline (SR: r=-0.68, p=0.0002; IVA: r=0.46, p=0.01), and during pacing (SR: r=-0.56, p=0.003; IVA: r=0.58, p=0.002). Both SR and IVA increased with pacing and isoprenaline (table 1), however the greatest % change was seen during isoprenaline infusion for IVA (p < 0.006) and SR (p < 0.0001).

Conclusion

SR enhances with increasing HR in children, demonstrating a relative HR dependence and a FFR. This is contrary to findings in adult studies, thus this study highlights that children show a different LV mechanical response to chronotropic effects and therefore caution should be use when extrapolating of adult findings to children.

Table 1. SR and IVA during baseline, atrial pacing and isoprenaline infusion

	Baseline	Pacing	Isoprenaline	p – value (B-P)	p – value (B-I)	p – value (P-I)
IVA	0.76 m/s², (0.5 to 1.1)	1.74 m/s², (1.3 to 2.1)	2.22 m/s², (1.8 to 2.9)	p < 0.0001	p < 0.0001	p < 0.007
SR	-0.9 %/s, (-0.7 to -1.1)	-1.0 %/s, (-0.9 to -1.2)	-1.9 %/s, (-1.5 to -2.1)	P < 0.0001	p < 0.0001	p < 0.0001

Funded By:

Abstract #: 22
Presenter: Jacqueline Ogilvie
Supervisor: Helly Goez
Title: Anti-NMDA Receptor Antibodies: a possible cause for autistic regression?
Authors: Jacqueline Ogilvie, Helly Goez, Basma Al-Jabri, Lonnie Zwaigenbaum, Cara Dosman, Brenda Clark, Keith Goulden, Marvin Fritzler
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

INTRODUCTION: Autism Spectrum Disorders (ASD) are common neurodevelopmental disorders that present in childhood. Children with ASD have qualitative deficits in social interaction and communication as well as restricted interests and repetitive behaviours. Interestingly, children present along two different trajectories: those who have atypical social development from an early age and those who present with developmental regression, typically in social and communication skills between 12-24 months of age. Our research team previously described a child who presented with classic symptoms of ASD and regression that was found to be due to anti-NMDA-receptor antibodies. The child was successfully treated and regained his skills. Given that the cause for regression in ASD is unknown, we sought to test a cohort of children with ASD and a history of regression for the presence of anti-NMDA-receptor antibodies.

METHODS: We conducted a retrospective case series to identify children with ASD and a history of developmental regression, as defined in the Autism Diagnostic Interview – Revised. We identified children through the Preschool Assessment Service (PAS) at the Glenrose hospital. One team member reviewed all PAS clinic notes from 2012 and 2013 for eligible participants. Twenty-five (25) children were enrolled and underwent lab testing for serum anti-NMDA-receptor antibodies. Parents provided information about their child and family history through a questionnaire. All samples were processed using the cell-based assay for antibody detection to the NMDA receptor NR1 subunit.

RESULTS ***Serum Samples:*** None of the children were positive for anti-NMDA antibodies

Descriptive Statistics:

Onset of first concern (mean age)	20.5 months
Age of first medical assessment (mean age)	26.3 months
Sleep problems at time of regression	68%
Preceding illness prior to regression	50%
Family history of ASD	25%
Family history of Autoimmune disorder	40%

CONCLUSIONS: In a series of 25 children with ASD and regression, none were found to have serum anti-NMDA receptor antibodies. Sleep problems and preceding illness were common findings at the time of regression, affecting more than half of the children. Anti-NMDA receptor antibodies appear to be an unlikely etiology for autistic regression, but our small sample size as well as the time from the first concern to testing for the presence of serum antibodies, may have limited our ability to detect further cases. Clinicians could consider anti-NMDA testing in children who have an atypical presentation of ASD and regression, including seizures or abnormal movements, desirably closer to the acute presentation.

Funded By: Trainee Research Grant

Abstract #: 23
Presenter: Merlin Pinto
Supervisor: Georg Schmolzer
Title: Cardiovascular effects of epinephrine during neonatal cardiopulmonary resuscitation in a piglet model
Authors: Merlin Pinto, Elliott Li, Min Lu, Tze- Fun Lee, Megan O'Reilly, Po-Yin Cheung, Georg Schmolzer
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Mixed Methods

Background

Neonatal resuscitation guidelines recommend epinephrine during cardiopulmonary resuscitation (CPR) to elevate the coronary perfusion pressure (CPP) to allow more oxygenated blood enter the coronary arteries to improve myocardial blood flow. However, no study has assessed the effects of epinephrine on cardiac function.

Objective: To determine cardiovascular effects of epinephrine administration during resuscitation of newborn piglets with asphyxia.

Materials and Methods:

Newborn piglets (n=8) were exposed to hypoxia and once bradycardia was achieved chest compression (CC) using 3:1 compression:ventilation ratio was started. Epinephrine was administered if heart rate remained < 60/min with a max of 4 doses until either return of spontaneous circulation (heart rate >150/min for 15s) or death. A Millar™ catheter (AD Instruments, Dunedin, New Zealand) was placed in the left ventricle to measure cardiac output (CO), stroke volume (SV), and ejection fraction (EF). Measurements were taken at baseline (BL), during positive pressure ventilation, during CC, and after each epinephrine (Epi1-4) administration.

Results: Mean (SD) age of piglets was 2 (1) days and weight was 2037 (250)g. EF, mean arterial blood pressure (MAP) and dP/dt, but not CO or SV, significantly increased during CC and Epi1-4 (vs. BL). There were significant increases in MAP after Epi2 and dv/dt after Epi4, compared to BL values, while all other parameters were similar.

	BL	CC	Epi 1-4
EF (%)	11	24 (p=0.048)	26-42 (p<0.02)
MAP (mmHg)	19	49 (p<0.001)	56-67 (p<0.001)
dP/dt (mmHg/s)	1144	3444 (p=0.002)	4066-9540 (p<0.002)

Conclusion: Epinephrine during neonatal CPR is in part is related to a vasoconstrictive action leading to increased MAP and thus CPP, which is important for the myocardial recovery following asphyxia in the newborn heart

Funded By: University of Alberta, Stollery Children s Hospital

Abstract #: 24
Presenter: M. Florencia Ricci
Supervisor: Charlene Robertson
Title: Gastrostomy Tube Feeding after Neonatal Complex Cardiac Surgery identifies the need for Early Developmental Intervention
Authors: M. Florencia Ricci, Gwen Alton, David Ross, Bryan Dicken, Diane Moddemann, Reg Sauve, Ari Joffe, Charlene Robertson
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

INTRODUCTION: Early Developmental Intervention (EDI) programs assist children who have, or are at risk of having, developmental delay. EDI is known to positively impact outcomes across developmental domains, including health, language, cognitive and social/emotional development as well as family empowerment. Gastrostomy tube feeding (GTF) is indicated in children with swallowing difficulties to prevent aspiration and lung disease, and to enhance growth and nutrition. We hypothesized the presence of GTF in an infant at any time after the first complex cardiac surgery (CCS) could potentially be used as a simple identifier for the presence of developmental delay and need for EDI. The main objective of this study is to compare the proportion of different types of developmental delay in CCS survivors with and without GTF. A secondary objective of the present study is to explore and better understand pre- and post-CCS predictors of GTF that might help improve care and counseling of these children's families.

METHODS: This comparison study of two groups within an inception cohort included 334 CCS survivors after cardio-pulmonary bypass at ≤6 weeks of age (2005- 2012) who did not require extracorporeal membrane oxygenation or heart transplantation. Children were assessed at 21±3 months with the Bayley Scales of Infant and Toddler Development, 3rd edition and the Adaptive Behavior Assessment System, 2nd edition: General Adaptive Composite (GAC). Delay was determined by scores >2 SD below mean. Chi-square test compared groups. Predictors of GTF were analyzed using Multiple Logistic Regression analysis, results expressed as Odds Ratio (OR) with 95% Confidence Interval (CI).

RESULTS: 67/334 (20%) of survivors had GTF any time before the 21-month assessment. Developmental delays in children with GTF were: cognitive 16(24%), motor 18(27%), language 24(36%) vs. without GTF 7(3%), 8(3%) and 32(12%) respectively (P<0.001). Gastrostomy group had almost eight times the number of children delayed on the GAC. Independent OR for GTF are: presence of a chromosomal abnormality, OR:4.6(95%CI:1.8,12.0)(P=0.002), single ventricle anatomy, OR:3.4(95%CI:1.7, 6.8)(P<0.001), total postoperative days of open sternum, OR:1.15(95%CI: 1.1,1.3)(P=0.031) and total number of hospital days at CCS, OR:1.03(95%CI:1.1, 1.04)(P=0.002).

CONCLUSIONS: GTF identifies CCS survivors at risk for delay, who would benefit from EDI. The described acute care predictors should guide efforts to improve the care of these children.

Funded By: Support services

Abstract #: 25
Presenter: Mosarrat Qureshi
Supervisor:
Title: Does Hyponatremia in Asphyxiated Newborn infants correlate with incidence of death or disability?
Authors: Mosarrat Qureshi, Mohamed Elboraee, Leonora Hendson, Amber Reichert, Ernest Philipos
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Mixed Methods

Introduction: Although therapeutic hypothermia (TH) in neonates with moderate or severe hypoxic ischemic encephalopathy (HIE) is a standard component of the neonatal intensive care, hyponatremia has been reported between 33% and 44%, with a trend towards a higher incidence in cooled patients. Hyponatremia in term newborn infants with HIE has been associated with death or severe disability at 18 months of age.

Objective: To find out the incidence, degree and the duration of hyponatremia, its pathophysiology, correlation with HIE severity, and predictive value in short and long term outcome.

Methods: Data were abstracted for all infants > 35 weeks gestational age (GA) treated in the Northern Alberta Neonatal Program with moderate to severe HIE (HIE II/III) from Jan 1, 2006 to Dec 31, 2012. Growth restricted and those with major congenital anomalies were excluded from analysis. Data fields included patient demographics, peripartum factors, serum sodium, Input/output data, weight change and mortality as well as disability comprising of Cerebral palsy, cognitive delay, hearing loss and blindness at 18 months and 3 years of age. The 2 groups identified were: Gp1= infants with any hyponatremia <130mmol/L during the 1st 96 hours of life, while Gp 2= infants with sodium ≥130mmol/L during the 1st 96 hours of life. Univariate and multivariable regression analyses compared the 2 groups.

Results: Of 170 babies, mean GA 39.1±1.6 weeks and mean birth weight 3.354±0.64kg. 72 (46%) infants were in Gp1, 86 (54%) infants were in Gp2 while data was missing for 9 infants. No significant association between TH and hyponatremia was observed (p=0.08).The incidence of hyponatremia was statistically significantly different during 25-36 hours of age (41%)Vs 37-48 hours (36%) (p=0.0138). Any hyponatremia during the 1st 4 days of life, was statistically significantly related to a composite outcome of death/ disability (p 0.027). Male gender, Apgar score<5 at 5 min and Cord pH or pH in first blood gas <7 were found to be statistically significantly (p<0.05)correlated with composite outcome of death or disability. Multivariable analysis showed infants in Gp 1 had an odds ratio of 2.4 (95%CI 1.19, 4.81) for composite outcome of death or disability (p0.014).

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Conclusions: TH did not affect the overall sodium levels in either groups. Any hyponatremia correlated well with composite outcome of death or disability at 18 months and 3 years of age. The incidence of hyponatremia was highest during 25-36 hours of age. As such careful fluid management during early in the course of treatment should be exercised.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 26
Presenter: Quang Vo
Supervisor: Edmond Lou
Title: Intra- and inter-reliability of the Cobb angle measurements on the plane of maximal curvature in adolescents with idiopathic scoliosis
Authors: Quang Vo, Zhitao Zhong, Lawrence H. Le, Edmond Lou
Affiliations: University of Alberta
Research Activity: Scoliosis
Investigation Type: Quantitative Research

Introduction: Adolescent Idiopathic Scoliosis (AIS) is a three-dimensional deformity of the spine associated with axial vertebral rotation. Cobb angle (CA) measurement is currently a gold standard to diagnose scoliosis and the magnitude of CA reflects the severity of the deformity. However, the traditional X-ray technology restricts orthopedic surgeons to use the 2D postero-anterior (PA) radiographs to measure the CA, which underestimates its true value. The true CA should be obtained on the plane of maximal curvature (PMC), which can be reconstructed using 3D spinal images. Our group has developed an algorithm to reconstruct 3D spinal images using ultrasound (US) data. A phantom study has demonstrated the discrepancy of the PMC CA was 4.2° ± 1.1° between the ultrasound and CT measurements.

Purpose: The objective of this *in-vivo* study was to evaluate the reliability of the Cobb angle measurement on the PMC using ultrasound images.

Methods: Ten AIS-diagnosed subjects with their major Cobb angles less than 40° were recruited and scanned in a standard standing position. A software was developed to reconstruct a 3D spinal image using 2D frames. The apical vertebral rotation along the curve was first calculated on the 3D image. Based on this rotation, the PMC was then determined, on which the CA was measured. Two raters, the software developer with 2-year ultrasound measurement experience (rater 1) and a naive rater (rater 2), were blinded with patient information and measured the CA twice in one week apart. Prior to the measurements, the naive rater was trained until he was confident to perform the measurements. To determine the reliability, the intra-class and inter-class correlation coefficients, and the Pearson correlation were calculated by comparing the averaged measurements of both raters.

Results: Among the ten subjects, two subjects' data sets were excluded due to the low image quality. Eleven curves were identified and measured by both raters. The intra-reliability coefficients for rater 1 and 2 were 0.966 and 0.924, respectively. The inter-reliability and the Pearson correlation coefficients between rater 1 and 2 were 0.884 and 0.909, respectively. These results indicated the Cobb angle measurements from the PMC were highly reliable.

Conclusions: This was the first *in-vivo* study that could deploy a non-ionizing radiation approach to measure the CA on the PMC. Although the intra- and inter- reliabilities of the measurements were high, the accuracy of *in-vivo* measurements needs to be established before the US approach can be applied in scoliosis clinics.

Funded By: Scoliosis Research Society, NSERC

women & children's health research institute

Abstract #: 27
Presenter: June Cheung
Supervisor: Lawrence Le
Title: Comparison of diagnostic ultrasound and direct measurement for examination of the periodontium: a systematic review
Authors: June Cheung, Kim-Cuong Nguyen, Neelambar Kaipatur, Paul Major, Lawrence Le
Affiliations: University of Alberta
Research Activity: Child and Youth / Women's Health : Dental Health (Radiology and Imaging)
Investigation Type: Quantitative Research

Introduction

The periodontium, which consists of the alveolar bone, cementum, gingiva and periodontal ligament, provides support for teeth. Current methods of examining the periodontium include direct probing, radiographs, cone-beam computed tomography and micro-computed tomography. However, these techniques are not ideal as they are either invasive or involve the use of ionizing radiation, which can be harmful to the subject. The use of diagnostic ultrasound, a non-invasive and non-ionizing procedure, has been investigated for its potential in imaging the periodontium.

The purpose of this systematic review is to examine the literature for studies that have compared ultrasound imaging to the "gold standard" of direct measurement in order to draw a conclusion about the accuracy and validity of ultrasonography as a diagnostic tool.

Method

In order to find all of the relevant studies, a systematic review was carried out. First, a detailed inclusion and exclusion criteria was agreed upon by the researchers. Following that, seven electronic databases were searched, including CINAHL, the Cochrane Library, EMBASE, LILACS, MEDLINE, PubMed and the Web of Science. In addition, Google Scholar was examined for grey literature. There were no language limitations or any other restrictions placed on the search. The search terms used were related to the periodontium, ultrasound imaging and direct measurement. The results from the database searches were then independently evaluated by two researchers according to the inclusion and exclusion criteria.

Results

From the initial set of 765 articles, a total of twenty-three studies fulfilled the criteria and were included in the systematic review. We are in the process of carrying out the data analysis. A risk of bias assessment will also be carried out for each included study to ensure that the data extracted from each study is reliable.

Conclusions

The importance of a systematic review cannot be understated as there is a wealth of data on this topic, but it lacks a unifying conclusion on the validity and accuracy of ultrasonography as a diagnostic tool for assessing the periodontium. The studies covered a wide array of periodontal measurements, including gingival thickness and sulcus depth. These measurements were also taken in a variety of subjects, including *ex vivo* porcine samples and *in vivo* human subjects. By organizing the studies according to the type of measurements carried out, a more accurate analysis of the results can be carried out.

Funded By: University of Alberta Faculty of Medicine

Abstract #: 28
Presenter: Yusuke Echigoya
Supervisor: Toshifumi Yokota
Title: Combined in silico and in vitro screening identifies a promising antisense drug candidate for exon 51 skipping therapy in Duchenne muscular dystrophy
Authors: Yusuke Echigoya, Bo Bao, Bailey Miskew, Joshua Lee, Aleksander Touznik, Toshifumi Yokota
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Quantitative Research

Introduction

Duchenne muscular dystrophy (DMD), the most prevalent lethal genetic disorder in boys, is caused by a lack of dystrophin protein due to mutations in the *dystrophin* (*DMD*) gene. Antisense oligonucleotide (AO)-mediated exon skipping, which can induce partly-functional dystrophin protein, has great potential for treating DMD. While clinical trials of AO-mediated exon skipping therapy such as eteplirsen (morpholino AO) and drisapersen (2'O-methyl-phosphorothioate AO) targeting exon 51 are ongoing, the levels of rescued dystrophin protein were not as high as those seen in milder Becker muscular dystrophy (BMD) patients.
Contributing to these issues may be related to two limitations of previous screening efforts: (1) rational algorithms to design AO sequences were not available, and (2) rescue of dystrophin protein expression by designed AOs could not be assessed, due to an absence of adequate DMD cell models.

Purpose: 1) To develop a robust *in silico* and *in vitro* screening system for identifying AO drug candidates. 2) To identify a new AO drug candidate in exon 51 skipping therapy that more effectively increases dystrophin protein expression than ones under clinical trials.

Methods

We designed 413 AOs targeting *DMD* exon 51 and predicted its exon skipping efficiency using our software algorithm. Based on the prediction, potentially effective AO sequences were selected and synthesized using morpholino chemistry. We generated a new DMD cell model, immortalized clonal DMD skeletal muscle cells, which differentiate well enough to produce a large amount of mutant dystrophin mRNA and accordingly make possible quantitative assessment of dystrophin protein induced after AO transfection. We examined the capability of the designed AOs to skip exon 51 and to rescue dystrophin protein.

Results

Our computational approach enabled to predict highly effective AO sequences for exon 51 skipping, and *in vitro* screening method allowed for quantitatively assessing rescued dystrophin protein. Accordingly, the combined screening system identified a promising new morpholino drug candidate for exon 51 skipping therapy which was up to 12 times more effective at skipping the exon, and over 4 times more effective at producing dystrophin protein compared to the eteplirsen sequence.

Conclusions

We established a combined *in silico* and *in vitro* screening system to identify AO drug candidates capable of restoring dystrophin protein expression for *DMD* mutations. Our new screening system could be also beneficial to find clinical AO candidates targeting other *DMD* exons and could be applied to other muscle diseases that can be potentially treated by exon skipping.

Funded By: Innovation Grant

Abstract #: 29
Presenter: Jennifer Hocking
Supervisor:
Title: Superior coloboma: a novel disease originating from a newly discovered feature of ocular development.
Authors: Jennifer Hocking, Jakub Famulski, Sonya Widen, Sophie Koch, Omri Weiss, Adi Inbal, Ordan Lehmann, Andrew Waskiewicz
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Quantitative Research

Introduction: Development of the eye begins with an optic vesicle bulging from the forebrain and then invaginating to form the optic cup. On the ventral side of the optic cup, a fissure opens temporarily to allow for the ingrowth of vasculature to nourish the developing retina and lens, and for exit of the optic nerve.
When the ventral (choroid) fissure fails to close, a cleft called coloboma remains in the inferior eye and can cause mild to severe vision defects.

We identified patients with the novel condition of superior coloboma, where the cleft is in the upper portion of the eye. We therefore hypothesized the presence of a fissure in the dorsal optic cup.

Methods: We used wildtype, mutant and transgenic zebrafish embryos, which develop ex vivo, to study the morphological development of the optic cup.

Results: We discovered a previously unknown dorsal ocular fissure (DOF) in the developing zebrafish eye, and used a variety of imaging techniques to confirm its presence. Given that a disruption in fissure closure may cause superior coloboma, we asked what signals are required for DOF closure. Notably, bone morphogenetic proteins (BMPs) are critical for patterning of the dorsal retina, and we found that reduced BMP signaling in *growth differentiation factor 6a (gdf6a*/*bmp13)*-deficient embryos results in delayed fissure closure. Further, adult *gdf6a* mutants occasionally display a superior coloboma, and one of the human superior coloboma patients carries a mutation in BMP receptor 1a. Sonic hedgehog (Shh) signaling from the ventral retina opposes BMP signaling in the dorsal retina, and *shh*-responsive genes are expanded in *gdf6a* mutants. Inhibiting Shh significantly rescued the persistent fissure phenotype in *gdf6a*-deficient embryos.

The function of the DOF could be to act as a conduit for blood vessel growth, similar to the choroid fissure. Indeed, we show evidence that the dorsal radial vessel (DRV) grows through the fissure on its way to the lens. Moreover, inhibition of Shh caused both early fissure closure and aberrant vessel growth.

Conclusion: We have identified the novel condition of superior coloboma, which we propose is caused by a developmental failure to close a dorsal ocular fissure. The fissure functions as a path for blood vessel growth, and its closure is regulated by a balance between dorsal BMP and ventral Shh signaling.

Funded By: CIHR, AIHS

women & children's health research institute

Abstract #: 30
Presenter: Aleksander Touznik
Supervisor: Toshifumi Yokota
Title: In vitro efficacy of novel phosphorodiamidate morpholino based antisense oligonucleotides for the treatment of spinal muscular atrophy
Authors: Aleksander Touznik, Yusuke Echigoya, Toshifumi Yokota
Affiliations: University of Alberta
Research Activity: Neuromuscular Disorders
Investigation Type: Mixed Methods

Introduction

Spinal muscular atrophy (SMA) is one of the most common autosomal recessive neuromuscular disorders affecting the motor neurons, usually results in rapid progression of muscle weakness, leading to death at a young age. SMA is caused by a deficiency in survival of motor neuron (SMN) protein due to a homozygous mutation of the S*MN1* gene. Humans contain a unique inverted duplication of the *SMN1* gene known as *SMN2*, which is described as a modifier of SMA phenotype, as it is capable of producing approximately 10% functional protein product. This deficiency is due to a new silencer site, which promotes the exclusion of exon 7 in the post-transcriptional mRNA. Our goal is to identify and develop novel antisense oligonucleotides (ASOs) that target splice silencers to enhance the inclusion of exon 7 in the *SMN2* gene using the neutrally charged and less toxic phosphorodiamidate morpholino oligomer (PMO) chemistry.

Methods

Using ASOs to "knock-up" the production of full-length protein made by the *SMN2* gene is a promising therapeutic approach to treat SMA. Antisense microwalk experiments suggested that ASO position and length play an important role in silencer suppression. We designed several 30-mer PMOs targeting various silencer sites within *SMN2* to try and develop a more specific and less toxic treatment for SMA. SMA patient fibroblasts were used to test all PMOs. RT-PCR and Western blotting was used to quantify exon 7 inclusion of post transcriptional mRNA, and SMN protein production, respectively.

Results

A splice silencer site on intron 7 was shown to be the most promising target site using the PMO based chemistry. RT-PCR analysis revealed that several PMOs transfected at 10 μM are capable of complete exon 7 inclusion in severe SMA patient fibroblasts. Western blot analysis supported these results, as treatments resulting in the greatest inclusion of exon 7 also showed the highest increase in full length and functional SMN protein production.

Conclusion

Fibroblasts obtained from SMA patients that were transfected with our newly designed PMOs demonstrated to have efficient enhancement of exon 7 inclusion. Cells treated with one of our 30-mer PMOs showed rescue of SMN production to near normal levels *in vitro*. One of the novel antisense oligonucleotides identified in this study can potentially offer improvement for treatment of SMA in the future.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 31
Presenter: Charlotte Usselman
Supervisor: Craig Steinback
Title: Hyperoxic breathing in young healthy women: Influence on sympathetic neural outflow
Authors: Charlotte Usselman, Byung Gyu Kim, Rachel Skow, Michael Stickland, Rshmi Khurana, Radha Chari, Colleen Julian, Sandra Davidge, Margie Davenport, Craig Steinback
Affiliations: University of Alberta
Research Activity: Women's Health: Cardiovascular Regulation
Investigation Type: Quantitative Research

Introduction

The sympathetic nervous system is intimately involved in the regulation of cardiovascular function, and changes in sympathetic outflow have been associated with the development of clinical cardiovascular pathologies, the majority of which are more prevalent in men than in women. Along those lines, recent evidence suggests that sex hormones exert an important influence over sympathetic nerve activity, although the mechanisms by which this interaction occurs remain to be fully elucidated. In this pilot study, we hypothesized that breathing air with high levels of oxygen (hyperoxia) would inhibit muscle sympathetic nerve activity (MSNA) in young, healthy women.

Methods

Participants were assessed during the early follicular phase of the menstrual cycle, with the exception of 2 individuals with hormone-secreting intrauterine devices (Mirena); these participants were tested at their convenience. Heart rate (HR; electrocardiogram), mean arterial pressure (MAP; Finometer), cardiac output (Q; ModelFlow), and MSNA (microneurography) were assessed in 12 women (age: 27 ± 5 yrs; BMI: 23 ± 2 kg/m^2) during 3 minutes of semi-recumbent rest followed by 3 minutes of breathing hyperoxic air. The hyperoxic period was divided into three 1-minute bins, and the bin corresponding to the nadir of the sympathetic signal was selected for all subsequent analyses.

Results

The breathing of hyperoxic air resulted in elevated ETO_2 (+300 ± 44 Torr; P<0.001) and decreased $ETCO_2$ (-10 ± 8 Torr; P<0.001). Respiration rate (-0.5 ± 0.8 breaths/min; P=0.01) and HR (-5 ± 3 bpm; P<0.001) were reduced while MAP (+1.2 ± 2.9 mmHg; P=0.07) and Q (-0.1 ± 0.4 L/min; P=0.2) were not altered from baseline by hyperoxia. Both MSNA burst frequency (-3 ± 3 bursts/min; P=0.001) and total MSNA (-86 ± 157 a.u.; P=0.03) were significantly reduced with hyperoxia. However, total peripheral resistance (TPR; MAP/Q) was increased during hyperoxia (+0.6 ± 1.0 mmHg/L/min; P=0.02).

Conclusions

These data indicate that breathing hyperoxic air is associated with an acute reduction of efferent sympathetic nerve activity. That the hyperoxic stimulus can lower MSNA in young healthy women, a population who tend to have lower resting MSNA relative to similarly aged men as well as individuals with cardiovascular disease, suggests that hyperoxia will likely be equally or more effective at lowering MSNA in populations with elevated resting MSNA. Ongoing research will determine the extent to which MSNA is lowered by hyperoxic breathing in individuals with hypertension.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 32
Presenter: Sarah Fung
Supervisor: Leslie Sadownik
Title: Impact of vulvar intraepithelial neoplasia on the quality of life of women
Authors: Sarah Fung, Lori Brotto, Leslie Sadownik
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Qualitative Research

Introduction (Purpose): Vulvar intraepithelial neoplasia (VIN) is a premalignant condition of the vulva that can progress to invasive vulvar carcinoma. VIN may be treated with excision, ablative (laser) therapy, or topical therapy. About one-third of women will develop recurrent VIN after treatment, requiring further treatment. Previous students have shown that vulvar surgery is associated with sexual dysfunction and depression. Our goal is to assess the impact of previously diagnosed and treated vulvar intraepithelial neoplasia (VIN) on women's quality of life.

Methods: This study is a retrospective chart review of women who had been diagnosed and treated for VIN and subsequently referred to the VIN follow-up clinic at a tertiary care academic centre. Clinic patients received a validated questionnaire to assess the impact of VIN on their quality of life. Data collection included reviewing completed questionnaires, nursing notes (collected with a standard questionnaire), and physician documentation. We used each patient's questionnaire responses to calculate their total VIN score, which ranged from 33 for a patient with no distress to 100 for a patient with maximum distress.

Results: 105 patients' charts were reviewed, of whom 83 completed the questionnaire. The mean age was 57 years old. 45% of patients reported feeling anxious, 22% reported feeling depressed, and 22% reported feeling embarrassed regarding VIN. 26% of patients who are not sexually active reported that this was due to VIN. 18% of patients reported that VIN affected their relationship with their partner "quite a bit" or "very much". A high VIN score was significantly associated with lower age (p=0.04). Disease characteristics including time since diagnosis, time since last treatment, total number of biopsies, and total number of treatments were not associated with VIN score.

Conclusions: Feelings of anxiety, depression, and embarrassment and negative effects on relationships are common among patients with VIN. Younger patients with VIN experience a greater adverse effect on their quality of life than older patients.

Funded By:

women & children's health research institute

Abstract #: 33
Presenter: Vrajesh Pandya
Supervisor: Dr. Ing Swie Goping
Title: Bcl-2 interacting killer (Bik) – A prognostic indicator of breast cancer patient outcomes
Authors: Vrajesh Pandya, Darryl Glubrecht, Larissa Vos, John Hanson, Judith Hugh, Sambasivarao Damaraju, John Mackey, Ing Swie Goping
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Quantitative Research

Introduction

Breast cancer in North-American women is the number one cause of cancer associated deaths. Cancer is a heterogeneous disease with many factors clouding accurate prediction of prognosis. Identification of biomarkers and their clinical validation will pave the way for a better understanding of cancer and eventually improve patient survival. Apoptosis and autophagy are cell death and cell survival pathways respectively that greatly determine neoplastic aggressiveness. BH-3 only proteins are central regulators of both these pathways and hence offer promise of biomarker discovery. We investigated expression levels of BH-3 only members in breast cancer patients and found that Bcl-2 interacting killer (Bik) is an independent and significant predictor of disease free and overall survival of patients. Notably, its correlation with increased mRNA levels of ATG5, a proven biomarker of autophagy in cancerous tissues, points towards an autophagy dependent tumor survival pathway.

Methods

Gene microarray plus protein tissue microarray analyses from primary breast cancer patient samples were performed to identify markers associated with clinical outcomes. Statistical analysis of gene and protein expression scores was performed with respect to recurrence free and overall survival of patients. Stable cell lines expressing Bik were generated to test the functional contribution of Bik to cancer cell survival. Western blotting and siRNA knock-down was performed according to standard protocols.

Results

In order to find significant survival predictors among BH-3 only members, we analyzed mRNA levels of 5 BH-3 only candidates alongside well known clinicopathological variables in 175 breast cancer patients. Through univariate Cox analysis we found Mitotic grade, Bik and Bid to be significantly associated with recurrence free survival. Interestingly Bik was the only independent variable retained upon multivariate Cox analysis. Further investigation against 3 anti- apoptotic Bcl-2 family members ruled out the possibility of stoichiometric compensation. Strikingly, uni- and multivariate analyses of Bik, Bcl-2 and Bad protein expression also established predictive power of Bik being independent of Bcl-2 and a fellow BH-3 member Bad. All this analysis proved a clear association of Bik with poor patient prognosis. Additional investigation of Bik gene expression against autophagy biomarker ATG5 revealed a Bik:ATG5 correlation. Indeed a subset of breast cancer cell lines stably expressing Bik suggested high autophagy levels.

Conclusions

BH-3 only protein Bik is an independent prognostic indicator for poor breast cancer patient survival. Bik may stimulate autophagy mediated survival pathways that contribute to clinical cancer aggressiveness.

Funded By:

Abstract #: 34
Presenter: Indrani Dutta
Supervisor: Lynne Postovit
Title: Can Gamma Delta T Cells Target Breast Cancer Stem Cells?
Authors: Indrani Dutta, Anais Medina, Gabrielle Siegers, Lynne Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Infection, Inflammation, Immunology
Investigation Type: Qualitative Research

Introduction

Gamma delta T cells (GDTc) are immunosurveillance cells comprising 2-5% of circulating lymphocytes in humans. Naturally anti-tumoral, GDTc recognize antigens directly; they are not major histocompatibility complex (MHC)-restricted, thus can kill targets rapidly without clonal expansion. GDTc respond to self- molecules signaling cellular stress; recognition and tumour lysis are mediated by the T cell antigen receptor and/or the natural killer receptor NKG2D. NKG2D ligands include UL16-binding proteins (ULBP) 1–4 and MHC-like proteins MICA and MICB, which are often upregulated on transformed cells. A major problem with current therapies is their inability to target cancer stem cells (CSC), a small cell population responsible for tumor maintenance, therapy resistance and cancer recurrence. Stem cells tend to have reduced MHC class I and NKG2D ligand expression, governed by epigenetic regulation. Yet, studies in colon and ovarian cancer have shown that GDTc can target CSC. We are investigating whether GDTc can overcome immune resistance to target breast cancer CSC.

Methods and Results

Our panel of human breast cancer cell lines shows a range of CSC (cell surface $CD44^{+}$ $CD24^{-}$): from 0.5% in MCF-7 to 89.8% in highly aggressive MDA-MB-231 cells.
Cytotoxicity experiments (Calcein AM-release assay) suggest an inverse correlation between GDTc cytotoxicity and CSC prevalence in breast cancer targets, with MDA-MB-231 most resistant to GDTc killing. We chose SUM149 cells as our model as they a mix of stem and non-stem cells. Preliminary data suggest that SUM149 comprise ~10% stem cells under normal culture conditions. We will sort CSCs *via* flow cytometry and monitor the kinetics of reversion back to the original heterogeneous population. These data will inform future cytotoxicity experiments. Defined time points will be chosen to test the ability of GDTc to target CSCs. Our preliminary cytotoxicity assay against the SUM149 bulk population yielded ~60% cell lysis when cells were incubated with GDTc at a 20:1 effector: target ratio for 4 hours. Furthermore, we will analyze ULBP1-4 and MICA/B expression levels on CSCs vs non-CSC SUM149 cells and perform blocking assays against specific tumour antigens to determine the cytotoxicity mechanism employed by GDTc.

Conclusions

We hypothesize that lower tumour antigen expression on CSCs, potentially due to epigenetic regulation, enables escape from GDTc killing. We aim to overcome this process to optimize GDTc killing of breast cancer CSC.

Funded By:

women & children's health research institute

Abstract #: 35
Presenter: Matthew Benesch
Supervisor: David Brindley
Title: Autotaxin is an inflammatory mediator and therapeutic target in thyroid cancer
Authors: Matthew Benesch, Yi Ko, Xiaoyun Tang, Jay Dewald, Ana Lopez-Campistrous, Yuan Zhao, Raymond Lai, Jonathan Curtis, David Brindley, Todd McMullen
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Quantitative Research

Introduction: The incidence of papillary thyroid cancer has doubled in the last 10 years and will overtake colorectal cancer as the fourth leading cancer diagnosis by 2030. Women are three times more likely to develop thyroid cancer than men. Although overall survival rates are excellent, thyroid cancer metastasizes in up to 40% of patients. Of this group, 20% are resistant to radioactive iodine, the mainstay therapy after surgery. Recent studies suggest inflammatory-mediated signaling promotes thyroid tumor growth and treatment resistance, but the mechanisms for this are poorly understood. We provide evidence that the lipid growth factor, lysophosphatidate (LPA), contributes to this problem. Extracellular LPA is produced by the secreted enzyme autotaxin from lysophosphatidylcholine. Autotaxin is important in tissue remodeling and wound repair but autotaxin is overproduced in many inflammatory diseases including cancers. LPA promotes cancer progression, metastasis and resistance to chemotherapy and radiotherapy. No cancer treatment currently targets LPA signaling and this provides an opportunity for introducing novel cancer therapies.

Methods: Autotaxin immunohistochemistry was performed on >200 paraffin-embedded patient specimens (primary tumors, benign masses, normal tissue). LPA concentrations in fresh tissues were measured by mass spectrometry and inflammatory mediators by enzyme-linked immunofluorescence assay (ELISA). The effect of autotaxin/LPA signaling on thyroid cancer tumor growth and inflammatory mediator production was evaluated in heterotopic xenograft mouse models using female SCID mice injected with 8305C and SW-579 thyroid cancer cells. Once tumors became palpable, mice were gavaged daily with either water or a novel oral ATX inhibitor, ONO-8430506, a (Ono Pharmaceuticals, Japan).

Results: 1) Autotaxin expression in metastatic deposits and primary carcinomas was 4-10-fold higher than in benign neoplasms or normal thyroid tissue. 2) Malignant tumors were distinguished from benign tumors by high tumour autotaxin, LPA levels and inflammatory mediators including IL1b, IL6, IL8, GMCSF, TNFa, CCL2, CXCL10 and PDGF-AA. 3) A vicious regulatory cycle occurs in which LPA increased the secretion of inflammatory modulators in papillary thyroid cancer cultures. Conversely, treating cancer cells with inflammatory modulators increased autotaxin secretion. 4) Blocking LPA signalling in mice with xenograft thyroid tumors using a potent autotaxin inhibitor decreased tumor volume, angiogenesis and inflammation by 50-60%.

Conclusions: This study demonstrates that the autotaxin/inflammatory cycleis a focal point for driving malignant thyroid tumour progression and possibly treatment resistance. Inhibiting autotaxin activity provides an effective and novel strategy for decreasing the inflammatory phenotype in thyroid carcinomas. This treatment should complement other treatment modalities and provide better therapy for a predominantly female cancer.

Funded By: Innovation Grant

Abstract #: 36
Presenter: Stephen Genuis
Supervisor: n/a
Title: Towards a Healthy Beginning: Elimination of Persistent Toxicants from the Mother's Body
Authors:
Affiliations: University of Alberta
Research Activity: Maternal Research : Fetal Origins of Adult Disease
Investigation Type: Quantitative Research

Introduction: The Pediatric Academic Societies recently commented that "*low level exposure to environmental toxicity may be impacting the functioning of the current generation.*" The medical literature is replete with evidence of widespread damage to child health resulting from low-level chemical toxicant exposure to the fetus during pregnancy as a result of maternal exposure and/or bioaccumulation. A variety of afflictions from autism to pediatric cancer have been linked, in many cases, to gestational toxicant exposure. Recent cord-blood studies confirm that most preborn children in the 21st century are being highly exposed to a multitude of pollutants. Evidence-based interventions to remove the internal dose of maternal toxicants prior to pregnancy show promise as a means to diminish maternal-fetal illness.

Methods: 20 patients with assorted health conditions were each assessed for blood, urine and sweat levels of 120 different chemical toxicants. We endeavored to determine if induced sweating might eliminate the burden of toxic chemicals from their body. Sweat was collected during exercise, regular sauna, and infra- red sauna therapy. Toxicological testing for the spectrum of adverse chemicals was undertaken using respective laboratory techniques modelled after the methodology used by the Centres for Disease Control.

Results: Various chemical toxicants, but nor all, can be eliminated prior to pregnancy by directed interventions such as induced sweating – which facilitates transdermal depuration.

Conclusion: Elimination of the burden of toxicants prior to pregnancy can prevent a whole host of maternal and enduring fetal complications. Preconception healthcare to educate young people about determinants of healthy maternal-fetal outcomes should become a new standard of care in maternal-fetal health services. Young women should be advised to avoid chemical exposure and to eliminate their internal dose of chemical toxicants as much as possible prior to conception.

Funded By: none

Abstract #: 37
Presenter: Ozlem Cankaya
Supervisor: N/A
Title: Experiences of Albertan Youth: Gender effects in ministry service use patterns
Authors: Ozlem Cankaya, Christine Werk, Navjot Lamba, Cecilia Bukutu, Saiful Kabir, Xinjie Cui, Leslie Twilley
Affiliations: Alberta Centre for Child Family and Community Research
Research Activity: Gender effects on government service use
Investigation Type: Quantitative Research

Introduction (purpose): The main purpose of this study was to examine the experiences of Albertan youth in 2008/09 in a single year with a focus on gender differences. Also, this study explored differences in service involvement for the least and most advantaged youth. Method: Administrative data from participating ministries (Education, Innovation and Advanced Education, Health, Human Services, and Justice and Solicitor General) were anonymously linked for all of Alberta's youth (12 to 24 years old). The data included information on services or programs provided by ministries such as payments to physicians for services, student enrolment data, and the type of criminal offence charge. Results: Socio-economic status, mental health status and educational achievement were critical benchmarks for understanding youth's profile in Alberta. The socio-economic status of Albertan youth was similar for males and females.
Approximately 20% of males and females were represented in both the lowest and highest socio-economic status neigbourhoods. While the percentage of youth with mental health conditions was stable across age for males, it increased with age for females. Young female students (12 to 14 years old) were slightly more likely to be meeting educational expectations than their male counterparts. Furthermore, more females (57%) than males pursued a post-secondary education and were more likely to be enrolled in degree-granting programs. A profile of the 2,281 least and 7,517 most advantaged Albertan youth between 12 and 17 years who were receiving provincial government services was generated. Least advantaged is defined here as youth who were performing below educational expectations in the K-12 education system, who had a mental health condition, and who were living in the lowest socio-economic status neighbourhoods. Most advantaged youth performed above educational expectations, did not have a mental health condition, and lived in the highest socio-economic status neighbourhoods. Female youth between 12 and 17 years tended to be more advantaged over same-age males with respect to their socio-economic status, mental health status, and educational achievement. Among the least advantaged youth, 43% were females, while among the most advantaged group 55% were females. Conclusions: Policy, program development, and evaluation can be informed by this unique body of evidence. Further research is building on these findings and methodology.

Funded By: Government of Alberta Ministries

women & children's health research institute

Abstract #: 38
Presenter: Shannon MacDonald
Supervisor: Suzanne Tough
Title: The Uptake and Determinants of Privately Funded Rotavirus Vaccine: A Bad News Story for Vulnerable Populations
Authors: Christopher Bell, Kimberley Simmonds
Affiliations: Other
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Background: Rotavirus vaccine can effectively prevent rotavirus gastroenteritis, a potentially serious disease, even in developed countries. Although rotavirus vaccine has been recommended by Canada's National Advisory Committee on Immunization since 2010, it is still not funded in some jurisdictions; Alberta added rotavirus to its publicly-funded program in June 2015. This retrospective population-based study assessed the epidemiology of rotavirus vaccine uptake in Alberta to determine the characteristics of families that purchased the vaccine privately.

Methods: Deterministic linkage of pharmaceutical dispensing, vital statistics, and public health insurance data determined vaccine coverage from 2008 to 2013. Multivariable logistic regression was used to assess characteristics of children who were immunized.

Results: Vaccine coverage ranged from 1% to 4% between 2008-2013, with 52% of vaccinated children completing the full vaccine series; 7.9% and 3.8% of children received doses before and after the recommended ages, respectively. Children who received ≥1 doses of the vaccine were more likely to have married mothers (adjusted odds ratio [aOR] 1.76, 95% CI1.64-1.88), fewer siblings (aOR 3.44, 95%CI 3.01-3.94), be non-First Nations (aOR 2.29, 95%CI 1.78-2.94), and be born prematurely (aOR 1.32, 95%CI 1.23-1.42). Income was a strong influence in urban areas, but not in rural regions, where coverage was lower overall.

Conclusions: Vaccine coverage in a privately-funded model was very low and left high risk populations unprotected. While this vaccine is now provided to all Alberta children, other jurisdictions have not yet implemented a publicly-funded program, and more unfunded vaccines are on the horizon. Failure to fund nationally recommended vaccines may lead to inequity in provision of preventative health care to vulnerable populations.

Funded By: CIHR & AIHS Fellowships

Abstract #: 39
Presenter: Todd Radostits
Supervisor: William Craig
Title: Convenience or proper use: referrals to the Stollery Pediatric Emergency Department
Authors: William Craig, Todd Radostits, Bruce Wright
Affiliations: University of Alberta
Research Activity: Paediatric emergency, Health resource utilization
Investigation Type: Quantitative Research

Introduction: Waiting times in EDs have been creeping up over the past 20 years. The main cause of this increase is overcrowding, and there are many factors that may cause this. As this has occurred there are messages in the media suggesting strongly that overcrowding is mostly due to inappropriate (or convenient) use of the emergency department coupled with a lack of primary care physicians. In our pediatric ED, it is the impression of staff physicians that many patients have been asked to attend the emergency by a health care provider. If this is true, then the ED is providing a consultant service, and should be funded for such activity. If in fact the ED has few referrals, and most of the patients do not have primary care physicians, then resources should perhaps be funneled into outpatient primary care.

The primary purpose of this study is to quantify the percentage of patients who have been referred to the ED by a health care provider. A secondary question is to explore if those who are referred in are sicker than those who are not referred in.

Methods: This is a prospective cross sectional study. All the families triaged while a research assistant is present are asked to participate. Exclusions include those brought to the ED by police or EMS. A random sample of participants are asked to give permission to review their emergency department visit after the fact. This will provide the data for the secondary question.

Results: The study started July 14th, 2014, and is still ongoing. 900 are currently enrolled. Of these, 382 (42.4%) were recommended to attend the ED. Seventy percent of these were referred in by four top groups: their physician (27.5%), Health Link (18.8%), Medicentre (14.9%) and another ED (9.2%). Only 22% came with a referral note. Ninety three percent (823/887) of the patients report having a primary care physician. Eighty seven percent attended because of an acute condition.

Conclusion: Our emergency is providing consultative care to 42% of our patients. The vast majority of patients (93%) have a primary care physician. This would imply that our emergency is fulfilling a real medical need within the health care system rather than providing a venue for convenient health care.

Funded By: Dept of Peds start up grant, and Medical School Student scholarship

Abstract #: 40
Presenter: Rachel Flynn
Supervisor: Shannon Scott
Title: Reasons for variation in care in management of childhood nephrotic syndrome in Canada.
Authors: Rachel Flynn, Shannon Scott, Susan Samuel; for the CHILDNEPH Team
Affiliations: University of Alberta
Research Activity: Childhood nephrotic syndrome
Investigation Type: Qualtitative Research

Introduction: Childhood nephrotic syndrome causes significant morbidity due to recurrent episodes of heavy proteinuria. Treatment protocols for childhood nephrotic syndrome are highly variable among physicians and care centres due to a poor evidence base for many management decisions. A lack of consistency in management of patients with nephrotic syndrome leads to poor satisfaction with care for patients and families. It is also not known whether variability in treatments affects patient outcomes.

Methods: The primary aim of our convergent mixed methods study is to determine centre, physician, and patient-level factors associated with treatment variation (e.g., cumulative steroid exposure and length of steroid treatment). Ten qualitative health care provider focus groups were conducted to provide an understanding of the attitudes, beliefs and local contextual factors driving care variation in care. The quantitative component of the study is a longitudinal observational cohort study of the clinical course and treatments of patients presenting with idiopathic childhood nephrotic syndrome across 12 sites in Canada. We will also recruit physicians caring for children with nephrotic syndrome and create a hierarchical dataset with patients grouped within physicians and physicians grouped within centers. Quantitative and qualitative results will be integrated for interpretation at the end of study, and will collectively inform strategies to minimize variation in care and to improve overall provision of care in this patient population.

Results: Qualitative thematic data analysis from focus groups show that poor quality evidence, physician training, physicians' individual preferences, drug toxicity, patient characteristics and family preferences are some of the key factors driving practice variation. To date 143 patients, 38 physicians and 9 centres have been recruited into the quantitative study. Preliminary data evaluation shows significant variation in cumulative steroid dose prescribed for first presentation of nephrotic syndrome (4820 to 2168 mg/m2) and average days treated (82-169 days).

Conclusions: There is significant variability in steroid treatments for nephrotic syndrome across Canada. Physician factors, patient preferences and poor quality of evidence play a major role in causing these differences in practice.

Funded by: CIHR and Kidney Foundation of Canada

women & children's health research institute

Abstract #: 41
Presenter: Tara McGrath
Supervisor: Samina Ali
Title: A Qualitative Study of the Language of Satisfaction in Children
Authors: Tara McGrath, Samina Ali, Nadia Dow, Sarah Aziz, Molly Pilarski, Amy Drendel
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Pain Management
Investigation Type: Qualitative Research

Introduction: Measures of patient satisfaction are used to assess the effectiveness of pain management. Although satisfaction is a valuable outcome measure, there are no validated tools to quantify children's satisfaction. To develop such a tool, we must first understand which words children use to communicate satisfaction. Study goals were (A) to identify the words commonly used by children of different ages to communicate satisfaction, in general, and in the context of pain management, and (B) to determine if this vocabulary is similar to that used by their caregiver.

Methods: This study was a qualitative study of a convenience sample of 105 children-parent pairs, aged 3-16, who were evaluated at the Stollery Children's Hospital pediatric emergency department (PED) from July-November 2014. The children were interviewed using a semi-structured format involving a series of ten open-ended questions. These questions asked children to describe their feelings if 1) they receive something they want/need, 2) their expectations are met or not met in the ED, and 3) their pain was or was not relieved in the ED. A survey was also provided to the caregiver. The interviews were transcribed and grounded theory was employed for data coding and analysis.

Results: 105 child interviews were completed (53 females, 52 males, mean age 9.91 SD 3.71, age range 4-16). 105 caregiver surveys were completed (80 females, 25 males). Six child-caregiver pairs were removed due to incomplete data. "Good", "better," and "happy" were most commonly used by all children to express satisfaction with pain management (29%, 22% and 23%, respectively), with PED care (30%, 15% and 30%) and in general (15%, 4% and 50%). Children used the words "mad", "sad", "bad," and "not good" to communicate dissatisfaction with pain management (2%, 21%, 8% and 9% respectively), and with PED care (10%, 22%, 14% and 13%, respectively). Less than 50% of children were familiar with the meaning of the word 'satisfaction'. Some but not all of the words caregivers use were similar to their children.

Conclusion: The word "satisfaction" should not be used to communicate with children, as many lack understanding of the term. When analyses are complete, this study will outline the vocabulary that children use to describe satisfaction and will determine if this vocabulary varies with context, age and parental vocabulary. It will inform the development of a validated tool to measure children's satisfaction with pain management.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 42
Presenter: Tamara Germani
Supervisor: Lonnie Zwaigenbaum
Title: Stakeholder Perspectives' on Social Participation in Pre-School Children with Autism Spectrum Disorder
Authors: Tamara Germani, Joyce Magill-Evans, Lonnie Zwaigenbaum
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Mixed Methods

Introduction (Purpose): *Social participation* for children with disabilities considered the ultimate aim of rehabilitation. To date, the perspectives of stakeholders' have been missing in the refinement of this construct. Thus, the primary aim of this study was to refine the construct of *social participation* for pre-school children with Autism Spectrum Disorder (ASD) using stakeholders' perspectives. The secondary aim was to understand the facilitators and barriers experienced during the promotion of social participation.

Methods: A web-based survey was circulated across Canada through purposeful snowball sampling. Stakeholders were identified as clinicians or educators with over 2 years experience working with pre-school children with ASD. In addition, families were identified as stakeholders if they had a least one child with ASD less than 8 years old. Quantitative analysis was analyzed using frequency counting and qualitative analysis was analyzed using inductive content analysis.

Results: Analysis of 75 stakeholders (clinicians, educators and parents) revealed the mostly highly ranked construct was regulation of behaviours to moderate interactions during cooperative and complex play. Further, inductive qualitative analysis revealed that parents and professionals used intrinsic motivation strategies and contingency management to promote social participation. Disruptive and repetitive behaviours were seen to most negatively impact social participation while familiarity of persons or environments facilitated social participation. Barriers to social participation often included sensory elements; disruptive and repetitive behaviours while facilitators often included the child's familiarity with environment or individuals.

Conclusions: Findings suggest that stakeholders' view the construct of social participation as the cooperative and complex engagement of activities with peers requiring the internal regulation of behaviours.

Funded By: Support services

Abstract #: 43
Presenter: Nicholas Avdimiretz
Supervisor: Simon Urschel
Title: Allergies and autoimmune disorders in children after heart transplantation
Authors: Nicholas Avdimiretz, Stefanie Seitz, Simon Urschel
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction:

Heart transplantation is a life-saving intervention in children with end-stage heart failure or congenital heart disease. Children require lifelong immune suppression and sometimes induction with anti-thymocyte globulin (ATG) to prevent rejection. Many undergo incidental thymectomy for exposure of the operating field during transplant. Thymectomy and immune suppression result in altered T-cell repertoires, which could lead to atopic and autoimmune diseases. We hypothesized that transplantation in early childhood, combining thymectomy and immune suppression, increases the risk of development or worsening of atopic or autoimmune disease.

Methods:

We conducted a cross-sectional study of heart transplant patients aged ≤ 18 years at the Stollery Children's Hospital. Data was obtained via interview and
medical records: including diagnosis, age at transplant, induction, ABO compatibility, and development and severity of atopic or autoimmune disease. Thymectomy was presumed for patients having had transplant or cardiac surgery ≤ 12 months of age. Variables were compared using the Fisher's exact test and Mann-Whitney U test.

Results:

Overall, 21 patients were included. Age at transplant ranged from 10 days to 15 years (mean 3.12 ± 3.77 years). Nine patients (43%) were transplanted ≤ 12 months of age, and 14 (67%) received thymectomy. ATG induction was used in 14 patients (67%).

A majority, 14/21 (67%), reported having any atopic disease post-transplant, all of whom reported onset or worsening post-transplantation. Most common were eczema (9/21, 43%) and asthma (7/21, 33%). Patients receiving thymectomy were significantly more likely to have asthma (p=0.018), and significantly more likely to report asthma worsening post-transplant (p=0.045). Other atopic diseases were not significantly affected by thymectomy. Patients with worsening of asthma post-transplant were transplanted at a significantly younger age (p=0.040). ATG induction did not significantly impact atopy. One patient had celiac disease; no other autoimmune disease was found. Anemia was reported in 38% post-transplant; however, this was not associated with ABO compatibility and was likely non-hemolytic.

Conclusions:

Atopic diseases are common in children following heart transplantation. Compared to the general population, there is a higher prevalence of eczema (43% *vs* 11%) and asthma (33% *vs* 9%). Thymectomy is associated with increased development or worsening of atopic symptoms, especially asthma, probably due to altered T-cell repertoires. Younger age at transplant is also associated with atopic disorders, which may be confounded by thymectomy or indicate disturbance of the immune balance during development of self-tolerance. Immunological studies are required to explore the mechanisms of immune dysbalance in this population.

Funded By:

women & children's health research institute

Abstract #: 44
Presenter: Erin Boschee
Supervisor: Justine Turner
Title: Prediction of esophageal and gastric histology by endoscopic diagnosis during upper endoscopy in pediatric celiac disease
Authors: Erin Boschee, Jason Yap, Justine Turner
Affiliations: University of Alberta
Research Activity:
Investigation Type: Quantitative Research

Introduction: Celiac disease (CD) is the most common autoimmune enteropathy in children. Recent guidelines suggest that diagnosis may be possible without biopsy in select pediatric patients, but concerns exist over the potential for missing alternate tissue diagnoses. However, the frequency of endoscopic and histological abnormalities in intestinal sites other than duodenum in patients with CD has yet to be specifically studied. The aim of this study was to determine the sensitivity of endoscopic appearance for predicting normal histology at sites other than the duodenum.

Methods: The study retrospectively reviewed endoscopic and biopsy findings in patients diagnosed with CD at Stollery Children's Hospital from 2010-2012. The primary outcome was the diagnostic performance of endoscopic findings in predicting normal histology of the esophagus and stomach. A secondary outcome was the prevalence of other esophageal and gastric diagnoses.

Results: There were 140 patients included in the study (61.4% female, 38.6% male). The mean age at biopsy was 9.1 years, and the mean aTTG was 393.9.

Endoscopic appearance was reported as normal in the esophagus and stomach in 84.8% and 87.7% of patients, respectively. Abnormal endoscopic esophageal diagnoses included eosinophilic esophagitis (5.8%), esophagitis (5.1%), glycogenic acanthosis (1.4%), and non-specific abnormalities (2.9%). In the stomach, endoscopic abnormalities reported included gastritis (6.5%), pancreatic rest (0.7%), and non-specific abnormalities (5.1%). Biopsies were taken from the esophagus and stomach in 54.3% and 77.9% of patients, respectively. Histology was normal in 77.6% of esophageal and 87.2% of stomach specimens. Abnormal esophageal histologic results included eosinophilic esophagitis (10.5%), esophagitis (9.2%), glycogenic acanthosis (1.3%) and other non-specific abnormalities (1.3%). In the stomach, gastritis was reported in 12.8% of specimens.

The sensitivity and specificity of endoscopic diagnosis for predicting normal esophageal histology was 86.2% and 61.1%, respectively. In the stomach, the sensitivity was 88.3% and specificity was 26.7%. The positive predictive value of endoscopic diagnosis for predicting normal histology was 87.7% in the esophagus and 88.3% in the stomach.

Conclusions: This study suggests that, in the absence of gross endoscopic abnormalities, routine esophageal and gastric biopsies during upper endoscopy for pediatric CD are not needed. Endoscopic diagnosis is sufficiently sensitive to predict normal histology. This has cost and time saving applications for current clinical practice. Additionally, the prevalence of alternative diagnoses to CD was 22% in the esophagus and 13% in the stomach, suggesting that the risk of missing an additional tissue diagnosis with a non-biopsy approach to CD diagnosis is relatively low.

Funded By: Support services

women & children's health research institute

Abstract #: 45
Presenter: Moses Abobo
Supervisor: Justine Turner
Title: Prolonged nasoenteral tube feeding in children contradicts best practice guidelines
Authors: Moses Abobo, Justine Turner, Dawn Hartfield, Diana Mager
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Quantitative Research

Introduction: Tube feeding is an important means of nutritional support in the pediatric population. Expert consensus guidelines from the Canadian Pediatric Society and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition state that nasoenteral tube feeding is not appropriate for long term feeding, due to its known serious medical and psychosocial risks for patients and caregivers. Therefore, gastrostomy tubes are recommended for nutrition support predicted to last 3 months or more. A 2010 survey of health care providers at the Stollery Children's Hospital (Edmonton, Alberta) demonstrated that 73% of staff were unaware of guidelines for acceptable duration of nasoenteral tube feeding. Moreover, 43% of staff thought that a nasoenteral tube should be changed to a G-tube after 6 or more months. The objective of this study is to determine whether the duration of nasoenteral tube feeding in children at our centre is consistent with expert consensus guidelines.

Methods: Prospective chart review of all patients younger than 17 years of age referred from September to November 2013 for nasoenteral or gastrostomy tube feeding at the Stollery Children's Hospital was performed. Data was collected for one year from the time of referral.

Results: 47 children were referred for nutrition support during the study period. Excluding patients for early cessation of tube feeding or death, 40 children (67.5% male, 32.5% female) were included. The mean age was 13.5 months (range 0.5 months - 9 years). Inadequate intake (62%) and airway protection (28%) were the primary indications for tube feeding. Most referrals were made by general pediatricians (52.5%) and neonatologists (35%). 35 children were initially fed with a nasoenteral tube. 60% of these children were predicted to require tube feeding for months to years. However, 49% were fed with a nasoenteral for more than 3 months, with a mean duration of 4.4 months (0.25-12 months). 34% eventually underwent gastrostomy tube insertion, with a mean time to insertion of 3.3 months (0.25-12 months).

Conclusion: The duration of nasoenteral tube feeding in a significant proportion of children is longer than recommended by expert consensus guidelines. An important contributing factor is lack of knowledge amongst pediatric health care practitioners about existing best practice guidelines.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 46
Presenter: Daniela Migliarese Isaac
Supervisor: Dr. Justin M. Turner
Title: Anti-tissue transglutaminase normalization post diagnosis in children with celiac disease.
Authors: Daniela Migliarese Isaac, Seema Rajani, Justine M. Turner
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Quantitative Research

Introduction

Celiac disease (CD) is a common autoimmune enteropathy to gluten, leading to intestinal inflammation, villous atrophy, and malabsorption. Screening for CD screening involves anti-tissue transglutaminase (atTG) IgA levels, followed by intestinal biopsy for confirmation. A gluten-free diet (GFD) is required to alleviate symptoms, normalize atTG, and heal the intestinal mucosa in CD patients. We aimed to evaluate time to normalization of atTG in children post CD diagnosis, and examine factors impacting this time.

Methods

A retrospective chart review was completed to evaluate the rate of atTG normalization in pediatric CD patients attending the Stollery Pediatric Celiac Clinic from 2007 to 2014, and to assess clinical predictors that may impact time to resolution including: initial atTG, GFD compliance (GFDC), age at diagnosis, gender, ethnicity, presenting symptoms, medical comorbidities, and family history of CD. Univariate pearson correlation coefficients were calculated between each predictor variable and rate of successful atTG normalization. Significant predictors were combined using a multivariate binary logistic regression to determine independent predictors of atTG normalization, as well as a cox hazard regression analysis to determine predictors of time to normalization.

Results

339 patients met the inclusion criteria. Mean age was 9 years at diagnosis (range 1-17 years), with 64% females. Patients were followed for 6 months to 6 years. 83% of patients normalized atTG levels within the study time period. Mean time to normalization was 407 days (range 30 to 2540 days). On multivariate binary logistic regression analysis, T1DM and South Asian ethnicity were independent predictors of failure to normalize atTG (Exp[B]=0.228 [0.088-0.584], p=0.002; and Exp[B]=0.407 [0.179-0.923], p=0.031 respectively), with T1DM patients being four times less likely to normalize atTG. Conversely, GFDC was a strong predictor of atTG normalization (Exp[B]=7.013 [2.857-17.215]). Cox hazard regression demonstrated T1DM and South Asian ethnicity were also predictors of longer time to atTG normalization (Exp[B]=0.498 [0.304-0.817], p=0.006; and Exp[B]=0.673 [0.467-0.970], p=0.034 respectively). Patients with T1DM normalized atTG levels on average 240 days longer than those without.

Conclusions

There is a wide variation of rate and time to atTG normalization in children with CD. GFDC is the strongest predictor of early normalization. Patients with T1DM and South Asians are less likely to normalize atTG levels, and have longer time to normalization. This highlights the need for closer attention and education for these high-risk populations.

Funded By: Trainee Research Grant

Abstract #: 47
Presenter: Jawad Alzamil
Supervisor: Todd Alexander
Title: Identification of the Claudin-14 Promoter and Calcium Sensing Receptor (CaSR) Responsive Elements.
Authors: Jawad Alzamil, Wanling Pan, Todd Alexander
Affiliations: University of Alberta
Research Activity: Nephrology
Investigation Type: Quantitative Research

Introduction:

One in ten Canadians will have a kidney stone during their life. Kidney stones cause significant pain and are expensive to treat due to recurrent emergency room visits and surgeries. The majority of kidney stones are composed of calcium and the greatest risk factor for kidney stones is hypercalciuria (i.e. urine with excess calcium), for which the etiology is unknown. A recent GWAS linked hypercalciuria to claudin-14, a gene we have shown increases expression in response to a calcium load, thereby inducing calciuria. Given this relationship we set out to 1) identify the claudin-14 promoter and 2) identify calcium sensing receptor (CaSR) sensitive signaling elements.

Methods:

To this end, we performed quantitative RT-PCR on the 5' untranslated regions of the 3 mouse claudin-14 variants and found that the expression of the first variant increases after CaSR activation. *In silico* studies comparing 5' of the 5' UTR of multiple species identified a highly homologous 25 bp region approximately 400 bp 5' of transcript variant-1, predicted to have promoter activity. We therefore cloned between 500-1500 bp 5' of the 5' UTR of the mouse variant 1 into the pGL3 Basic and Enhancer luciferase reporter constructs. As a positive control we cloned the SV40 promoter. We then expressed these constructs in both a HEK293 cell line and another renal tubular cell line over expressing the CaSR (OK-CaSR).

Results:

Constructs containing 500, 700, 1000 or 1200 bp 5' of the 5' UTR of the mcldn-14 V1 didn't show any promoter activity when transfected into OK-CaSR cell lines. In contrast, the construct containing the 1500 bp fragment 5' of the 5' UTR of mcldn-14 V1 demonstrates promoter activity when transfected into both HEK293 and OK-CaSR cell lines and responds to CaSR activation in the OK-CaSR cell line.

Conclusion:

We therefore conclude that the claudin-14 promoter is located between 1200 (*exact length = 1243 bp*) – 1500 (*exact length = 1340 bp*) 5' to the 5'UTR of variant 1 and responds to CaSR activation. Future experiments will delineate the mechanism by which claudin-14 is regulated via this promoter.

Funded By: CIHR, AIHS

women & children's health research institute

Abstract #: 48
Presenter: Salma Bahreinian
Supervisor: Anita Kozyrskyj
Title: Maternal depression and development of atopic disease in children
Authors: Salma Bahreinian, Matthew Dahl, Mariette Chartier, Marni Brownell, Nicole Letourneau, Anita Kozyrskyj
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: Asthma is the most common chronic respiratory condition in Canada, and new-onset asthma affects up to 10% of children in North America. Traditionally known risk factors for asthma cannot explain the shifting trend of childhood asthma prevalence in the past few decades, emerging a call for development of new causation theories. There are reports of associations between early life exposure to maternal depression and/or anxiety and the development of childhood asthma, mostly in small and high risk populations.

Purpose: To determine the association between maternal prenatal and postnatal distress and the development of allergic disease in general population of Canadian children.

Methods: This was a retrospective population-based cohort of all children born in Manitoba in 2004, to examine the likelihood of asthma and atopy in children exposed and not exposed to maternal distress in utero, during infancy and in later life. Information on prenatal exposures was collected by public health nurses during home visits within the baby's first week of life. Asthma and atopic dermatitis were diagnosed using health care administrative records of physician visits and prescription medications.

Results: Out of 12587 children, 18.9% were diagnosed with atopic dermatitis by the age of five and asthma was diagnosed for 7.1% by the age of five seven. Over 50% of mothers experienced depressive symptoms during their pregnancy, postpartum, or during the preschool years of their child. Prenatal and postnatal maternal distress were associated with increased risk of atopic dermatitis in offspring, ORs 1.27 (95% CI 1.11 - 1.46) and 1.28 (95% CI 1.11-1.48), respectively.
Prenatal maternal distress increased likelihood of asthma in children, OR 1.57 (95% CI 1.29-1.91). Postnatal maternal distress was associated with an increased risk of asthma, but this association did not reach the statistical significance, OR 1.23 (95% CI 0.99-1.54). These associations were not observed when maternal stress was limited to the first year post-partum. Findings were adjusted for known asthma risk factors such as sex, maternal asthma or atopy, urban residence, low birth weight and infant antibiotic use.

Conclusion: Maternal depression during and after pregnancy is a common health problem, and may affect fetal lung development and maturation of the infant immune system towards an allergic profile. These findings underline the importance of screening programs for maternal mental health; and indicate that early intervention programs for treatment of maternal postpartum depression may mitigate the risk of allergic conditions in offspring.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 49
Presenter: Una Conradi
Supervisor: Ari Joffe
Title: Publication bias in animal research studies presented at the Society for Critical Care Medicine 2008 Conference
Authors:
Affiliations: University of Alberta
Research Activity: Research Methodology
Investigation Type: Quantitative Research

Introduction: Publication bias is suggested indirectly in systematic reviews of animal research (AR). We aimed to determine a direct measure of publication bias by determining subsequent publication of abstracts presented at an international conference.

Methods: We selected 100 random (random-number generator) AR abstracts from the 2008 Society for Critical Care Medicine conference. Using a case report form and study manual, we recorded methodology and result variables from abstracts. We searched PubMed and EMBASE for the first two and last authors, and at least two MeSH keywords to screen for subsequent publication by June 2015. Methodology and result variables were recorded from publications to determine changes in reporting.

Results: 61% (95% CI 51-70%) abstracts were subsequently published after a median 19 [IQR 9-33, range 0-68] months. Abstracts were of low quality: randomized 27% (method and allocation concealment not described), blinded 0%, sample-size calculation 0%, specifying primary outcome 26%, numbers given with denominators 6%, stating number of animals used 47% (median 18; IQR 11-24; range 1-60), and having positive outcomes 90%, statistically significantly so 55%. The only predictor of subsequent publication was being an oral presentation (14/16 vs 47/84 published, p=0.024). Publications were of poor quality: randomized 24 (39%; method and allocation concealment not described), likely blinded 4 (7%), primary outcome specified 3 (5%), sample size calculation 0%, numbers given with denominators 20 (33%), and number of animals used stated 34 (56%; median 20; IQR 14-35, range 5-125). Some changes from the abstract to publication occurred: from non-randomized to randomized 12 (20%), from non-blinded to blinded 4 (7%), from negative to positive outcomes 5 (8%), from having to not having primary outcome 10 (16%), from non-statistically to statistically significant 23 (38%), and to using fewer (3, 9%) or more (10, 29%; by median 14, IQR 5-25) animals. Post-hoc we used the combined abstract and, when available, publication data to update the analysis for predictors of publication: quality indicators (randomized, blinded) were not predictive, but having positive outcomes (published 61/61, unpublished 34/39; p=0.004), or statistically significant results (published 58/61, unpublished 20/39; p<0.001) were predictive.

Conclusions: Only 61% (95% CI 51-70%) of AR abstracts are subsequently published. Being an oral presentation, finally having positive outcomes, and finally having statistically significant results are predictors of publication. Publication bias is prevalent in critical care AR- animals are harmed without benefit, and with potential harm (misleading literature reviews), to humans.

Funded By: University of Alberta, Faculty of Medicine

Abstract #: 50
Presenter: Robin Featherstone
Supervisor: Lisa Hartling
Title: Knowledge Pyramids: an integrated knowledge translation strategy to inform clinical care
Authors: Lisa Hartling, Robin Featherstone, Carly Leggett, Lisa Knisley, Mona Jabbour, David Johnson, Terry Klassen, Shannon Scott
Affiliations: University of Alberta
Research Activity: Knowledge translation for pediatric emergency medicine
Investigation Type: Mixed Methods

Introduction: Translating Emergency Knowledge for Kids (TREKK) is a National Centre of Excellence in Knowledge Mobilization that was established in 2011 to address knowledge needs related to the care of children in general emergency departments across Canada. One of TREKK's platforms is knowledge synthesis through which we collate and synthesize evidence to inform clinical care. We developed the concept of knowledge pyramids to provide stakeholders with varying levels of evidence according to their information needs.

Methods: The knowledge pyramids are based on priority conditions identified through a national survey involving 1,471 health care professionals at 32 general emergency departments across Canada. We developed a national process to synthesize existing knowledge. In brief, a research librarian searches the literature to identify key resources relevant to a priority topic. A content expert guides the search and selects the most relevant resources for further synthesis. The knowledge broker works with the researcher to create user-friendly tools that provide quick and reliable information. The TREKK executive and steering committees approve materials prior to posting on trekk.ca. The tools and materials are presented in "knowledge pyramids" which provide increasing levels of detail: the top of the pyramid represents the most condensed and summarized information that can be used at the bedside in emergency settings. Moving down the pyramid, data become more detailed - from clinical pathways/practice guidelines, summaries and overviews of systematic reviews, to systematic reviews and finally to key studies at the bottom.

Results: To date we have completed 10 knowledge pyramids on: bronchiolitis, concussion, croup, diabetic ketoacidosis, fractures, gastroenteritis, multiple trauma, procedural sedation, sepsis, severe head injury. These comprise 14 bottom line recommendations (1-2 page documents providing key facts and recommendations on diagnosis and treatment), 39 clinical pathways and guidelines, 29 summaries and overviews of reviews, 42 systematic reviews, and 111 key studies. We gathered feedback from 35 end-users on pilot versions of three knowledge pyramids. The response was positive with 91% indicating they would use the resources for their work in the emergency department.

Conclusions: We created the knowledge pyramid format with end-users in response to their request for varying levels of information detail. Currently, healthcare professionals have instant access via trekk.ca to a range of evidence on conditions they identified to be of priority. An integrated approach has allowed us to develop and refine knowledge tools to meet end-user needs and provide evidence to inform front-line clinical care.

Funded By: Partnership resources

women & children's health research institute

Abstract #: 51
Presenter: Michelle Foisy
Supervisor: Lisa Hartling
Title: What works and what's safe in pediatric emergency procedural sedation: an overview of reviews
Authors: Lisa Hartling, Andrea Milne, Michelle Foisy, Eddy Lang, Douglas Sinclair, Terry P Klassen, Lisa Evered
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Pain Management
Investigation Type: Quantitative Research

Introduction: Sedation is increasingly used to perform procedures on children in emergency departments (EDs). This overview of systematic reviews examines the safety and efficacy of sedative agents commonly used for procedural sedation in children in the ED or similar settings. **Methods:** We followed standard systematic review methods: comprehensive search; dual study selection, quality assessment, and data extraction. We included systematic reviews of children (1 month to 18 years) where the indication for sedation was procedure-related and performed in the ED. **Results:** Fourteen systematic reviews were included (210 primary studies). Most data were available for propofol (6 reviews/50,472 sedations) followed by ketamine (7/8,238), nitrous oxide (5/8,220) and midazolam (4/4,978). Inconsistent conclusions for propofol were reported across six reviews. Half concluded that propofol was sufficiently safe, while three reviews noted a higher occurrence of adverse events, particularly respiratory depression (upper range reported across studies was 1.1%; upper range reported across studies was 5.9% for hypotension). Efficacy of propofol was considered in four reviews and found adequate in three. Five reviews found ketamine to be efficacious and seven reviews showed it to be safe. All five reviews of nitrous oxide concluded it is safe (0.1% incidence of respiratory events); most found it effective in cooperative children. Four reviews of midazolam made varying recommendations. To be effective, midazolam should be combined with another agent which increases the risk of adverse events (upper range reported across studies was 9.1% for desaturation and 0.1% for hypotension). **Conclusions:** This comprehensive examination of an extensive body of literature shows consistent safety and efficacy for nitrous oxide and ketamine, with very rare significant adverse events for propofol.

Funded By:

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Abstract #: 52
Presenter: Mary Klute
Supervisor: Shannon Scott
Title: Assessing parental pain information needs related to their child's surgical procedure
Authors: Mary Klute, Leeann Lukenchuk, Kathy Reid, Shannon Scott
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Pain Management
Investigation Type: Mixed Methods

Introduction

Pediatric surgical patients will inherently experience some degree of postoperative pain and are at risk for inadequately managed pain. Despite advances in assessment and treatment of pediatric pain, significant numbers of hospitalized children continue to experience moderate to severe pain. Parents are key participants in their child's care in the hospital setting; their involvement in postoperative pain management is a vital link between the child and nursing staff. Assisting with children's postoperative pain within the unfamiliar and busy hospital environment is challenging for parents. Parental knowledge is one of the most important factors contributing to the under management of pediatric pain. It is imperative that nurses adequately assess parental information needs prior to their child's surgical procedure so that essential information is provided during the preoperative and postoperative periods. The literature identifies a lack of consistent tools to assess parental information needs. The purpose of this study is to identify surgical pain information needs from a parental perspective.

Methods

Data was collected via a written questionnaire administered near the time of the child's hospital discharge. Questions were developed from the existing literature. Two nurse practitioners from the Stollery Chronic and Acute Pain Services and one pediatric nurse researcher assessed the questionnaire's content validity. A quantitative, descriptive design was utilized to identify the types of pain information required by parents in addition to the perceived importance associated with each item; there were also open-ended questions to identify other pain information needs. Unit nurses initially approached parents who met the inclusion criteria regarding participation in the study. Inclusion criteria were: parents whose children (aged 0-17 years) have undergone an elective surgical procedure (either day or inpatient surgery) at the Stollery Children's Hospital, and who speak, read, and write English. A research assistant then approached parents and explained the study, obtained consent, and gave them a survey package. Quantitative and qualitative data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) and NVivo, respectively.

Results

We are presently in the data collection and analysis phases of this project.

Conclusion

This project was a pilot study, leading towards a future larger scale study to develop a tool for nurses to identify parental pain information needs. Addressing parental informational needs prior to pediatric surgery will enable parents to effectively participate in their child's postoperative pain management, and result in effective pain control for children and improved pediatric health care.

Funded By: CIHR Health Professional Student Award, AIHS Summer Studentship, and Faculty of Nursing Undergraduate Summer Student Research Aw

women & children's health research institute

Abstract #: 53
Presenter: Robyn Langevin
Supervisor: Lawrence Richer
Title: Technology perspectives
Authors: Robyn Langevin, Meghan Linsdell, Lawrence Richer
Affiliations: University of Alberta
Research Activity:
Investigation Type: Mixed Methods

Introduction: Technology has become an essential component of medical diagnosis and assessment that aims to enhance care that is received in hospitals around the world. Much like medications, the imaging used in pediatrics was designed for adults.While the literature on making medications child friendly is growing, there are few studies regarding the adaptation of technology for children. There is also minimal research on the level of understanding of children and their parents in regards to the exams ordered.In the absence of research, clinicians may not be providing appropriate information to families. **Methods:** This study examined the perspectives of parents and children when technology was used for their assessment and care through a standardized survey with open ended questions. **Results:** We found 96.5% of parents were provided with enough information to make a decision for their child in regards to imaging technologies. There was some misinterpretation of the technology and a portion of the population was not given information at the time of ordering the tests (12.3%). Some participants had worries about the safety of the tests (15.8%) including concerns about sedation and radiation.The study also examined issues from the children's perspective on their imagining. In some cases, we learned what made the child scared and caused the need to repeat the tests. Sixty-four percent of issues with the tests may have been prevented if more information was given beforehand and 36% were related to physical difficulties with the technology itself. We also found a gap between the number of times a patient had gone for their test and their parent's understanding of the technology. Of the parents of patients who went for the same kind of imaging at least five times, 40% were unable to correctly say what the imaging does. Using NVivo to qualitatively analyze participant responses, we found a recurring theme that parents use the idea of x rays as their basis of understanding for MRIs and CTs with the majority referencing pictures. **Conclusions:** Overall, the study reinforced that healthcare professionals are typically providing adequate information, but it suggests that key information may either missing or lost in translation. The study also serves to inform healthcare professionals on what patients perceive are the discomforts/risks of technological investigations.Future work in this area may include the creation of brochures or software to provide information to parents/patients to increase comfort levels and optimize the chances of a successful imaging tests.

Funded By: Summer Studentship

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Abstract #: 54
Presenter: Allison Norris
Supervisor: Shannon Scott
Title: Data Collection Issues: Experiences with Researching the Pediatric Chronic Pain Population
Authors: Allison Norris, Kathy Reid, Shannon Scott
Affiliations: University of Alberta
Research Activity: Child: Chronic Pain
Investigation Type: Qualitative Research

Introduction

Pediatric chronic pain is a significant issue for children, families, and health care professionals. Pediatric chronic pain is a continuous or recurrent pain that lasts for three months or longer. Studies indicate that the incidence rates of pediatric chronic pain range from 2.5% to 25%, and the most frequent types of chronic pain are headache, abdominal pain, and musculoskeletal pain. Children experience various issues associated with chronic pain, including fatigue, school absenteeism, and anxiety. Parents are also affected by their child's chronic pain, relating to their feelings of despair, exhaustion, and helplessness.

Methods

For our arts-based Knowledge Translation study, the issues that parents and children encounter with chronic pain have affected our study's data collection methods. In the first phase of our study, we have been conducting semi-structured interviews with parents and children to gather their narratives about pediatric chronic pain. During this time, we have encountered several challenges with data sampling, specifically with recruitment, setting up interviews, and the interviewing process. The purpose of this presentation is to share some of the strategies that our research team has employed to circumvent data sampling issues, such as how to set up an ideal interview environment with participants and how to be aware of parental or children's needs during interviews. In addition, we will share how the challenges that we have encountered have shaped our maximum variation purposive sample.

Conclusions

We aim to create a dialogue with other researchers who would like to share their experiences with data sampling issues, or strategies with interviewing children, parents, and families. Researchers must be aware of the various experiences that children and parents can encounter with any health issue, and consider how these experiences can affect the research process.

Funded By: Innovation Grant

Abstract #: 55
Presenter: Kassi Shave
Supervisor: Lisa Hartling
Title: Procedural Pain in Children: A qualitative study of parent experiences and information needs
Authors: Kassi Shave, Samina Ali, Shannon Scott, Lisa Hartling
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Pain Management
Investigation Type: Qualitative Research

Introduction (Purpose): Procedural pain makes up the majority of the average child's experience with acute pain. Poorly managed procedural pain can have short-term and long-term impacts on a child, which can extend and complicate both a procedure and the ED stay. There are many evidence-based physical, pharmacological, and psychological interventions available to manage pain and distress in children undergoing procedures; however, their use varies significantly across Canadian EDs. Knowledge translation (KT) interventions are essential to ensure the uptake of evidence in practice. The objective of this study is to actively collaborate with parents of children experiencing procedural pain in the ED, and gather information to inform the development of a KT tool on management strategies for procedural pain.

Methods: Qualitative semi-structured interviews will be conducted with a purposeful sample of parents of children who attend the ED at the *Stollery Children's Hospital.* Our target for this study will be children who have undergone IV placement or venipuncture in the past 4 hours. Parents of children ages 3 to 12 years will be included. Based on previous qualitative research, we anticipate approximately 10-15 interviews will be required to see saturation of the data. Questions will move from general to specific, with interviews later in the data collection period becoming increasingly focused. The interviews will be audio-recorded and transcribed verbatim. Data analysis will be facilitated through the use of NVIVO 10.

The key stakeholder for this research is Translating Emergency Knowledge for Kids (TREKK), a National Centre of Excellence in Knowledge Mobilization. TREKK has a family advisory group that provides input on all TREKK activities, and will be involved in all aspects of the proposed project.

Results: The results of this research are forthcoming.

Conclusions: This research will generate new knowledge through collaborative researcher-stakeholder partnerships, and form the foundation for the development of a KT tool that will empower patients and their caregivers to play an active role in their healthcare. Ensuring patient and parent access to essential health information is critical for enhanced, family-centered, healthcare delivery and improved child health outcomes.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 56
Presenter: Iram Usman
Supervisor: Dr. Rhonda Rosychuk
Title: An Examination of Spatial Scan Statistics for Time to Event Data
Authors: Iram Usman, Dr. Rhonda Rosychuk
Affiliations: University of Alberta
Research Activity: Spatial Scan Statistics
Investigation Type: Quantitative Research

Introduction

The spatial scan statistic (SSS) has been used for the identification of geographical clusters of higher numbers of cases of an illness than expected. Disease outbreaks in a geographic area are a typical example. These statistics can also identify geographic areas with longer time to events if the SSS uses appropriate distributions. This study focuses on developing a new SSS based on time to event data and illustrates the new and the existing SSS's on the administrative data from Alberta Health.

Methods

The SSS's for the exponential and Weibull distributions have been proposed by other authors. We propose the log-Weibull as an alternative distribution for the SSS. Further, we compare and contrast the three SSS's through simulation studies to investigate the power of detection of a potential cluster, the effect of right differential censoring, and the strength of detection of a true cluster. These SSS's are also illustrated to identify clusters of longer times to specialist (cardiology or internal medicine) visit after an emergency department (ED) presentation for atrial fibrillation (AFF) and flutter in Alberta during 2010-2011.

Results

The exponential, Weibull, and log-Weibull SSS's detected the same most likely cluster (e.g., Peace Country, Northern Lights, and Aspen regional Health Authorities) comprising of rural areas in northern Alberta with sparse or low population. The results suggest that people living in these northern rural areas may not have regular or quick access to the follow-up care to a specialist after ED presentation. The simulation studies indicate that the Weibull SSS has higher power to detect the true cluster than the exponential and log-Weibull SSS's when the data were simulated from the exponential, Weibull, gamma, and log-Normal distributions. The Weibull SSS's power and detection of true cluster under differential right censoring was the most similar across all data sets with different parameters.

Conclusions

The results from the exponential, Weibull, and log-Weibull SSS's show that, all distributions were capable of detecting the same most likely cluster for the patients presenting to ED for an AFF in Alberta, but the Weibull distribution had the highest power of detecting the potential cluster amongst all. This was true under all differential right censoring situations for each generated dataset.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 57
Presenter: Amy Zhang
Supervisor: Shannon Scott
Title: Evaluating approaches to parent engagement in knowledge translation and child health research
Authors: Amy Zhang, Lauren Albrecht, Shannon Scott
Affiliations: University of Alberta
Research Activity: Child and Youth Development: Knowledge Translation
Investigation Type: Qualitative Research

Introduction
Engaging parents and families in health research is critical to improve healthcare. Fundamental to engaging families is the development of innovative ways to present complex health information. Innovative knowledge translation tools are increasingly being seen as the best approach to bridge this gap and effective methods for engaging parents in the development of these tools are needed. Therefore movement toward greater family involvement and improved pediatric health care warrants the need for more evaluation and understanding of the most effective approaches of engaging parents in research. The goal of this study is to generate recommendations for researchers interested in engaging parents and families in health research.

Methods
Qualitative focus groups and interviews have been used to elicit experiences and opinions from four parent groups: 1) the Stollery Women's Network, an Alberta-based community organization interested in child health issues; 2) the Translating Emergency Knowledge for Kids (TREKK) Initiative Parent Advisory Group, a Manitoba-based community organization interested in pediatric emergency research; 3) previous participants from a CIHR-funded child health study (S.Scott & L. Hartling, co-PIs); and, 4) previous non-participants from the CIHR-funded child health study (S.Scott & L. Hartling, co-PIs). During June to July, 2015, different data collection methods have been used to engage with these groups, including: a tweet-up focus group, teleconference focus group, telephone interviews, and in-person interviews to reach out to a greater number of parents.

Results
We are presently in the data analysis phase of this project. Two focus groups have been conducted through a teleconference and a Tweet-up with TREKK (Translating Emergency Knowledge for Kids) n= 4 and the Stollery Women's Network n= 9, respectively. Nine individual interviews have also been completed, one occurring in-person and the other eight over the telephone. Thematic analysis highlights the barriers and facilitators for parent and family engagement in child health and knowledge translation research.

Conclusions
Understanding the most effective approaches of engaging parents and families in child health knowledge translation research leads to greater family involvement and improved pediatric care. Our findings will establish better methods or tools to engage parents in child health research.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 58
Presenter: Petya Koleva
Supervisor: Anita Kozyrskyj
Title: Functional aspects of infant gut microbial community by maternal pre-pregnancy weight
Authors: Petya Koleva, Theodore Konya, Julia Copeland, David S. Guttman, Rupasri Mandal, David Wishart, Malcolm R. Sears, Allan B. Becker, Haqq, Radha Chari, Padmaja Subbarao, Stuart E. Turvey, James A. Scott, Anita L. Kozyrskyj
Affiliations: University of Alberta
Research Activity: Maternal Research : Lung Development, Injury and Regeneration
Investigation Type: Qualitative Research

Introduction: Gut microbiota play an essential role in regulating metabolic processes and modulating host immunity. High-throughput 16S sequencing techniques have added new insight into gut compositional changes seen in infants born to overweight mothers. However, research is limited on the functional aspect of gut microbiota and their metabolic activity. Thus, the current study applied metagenomic sequencing and metabolomic techniques to characterize the infant gut microbiota function according to maternal pre-pregnancy overweight status. Methods: A sub-set of 190 mothers and their full-term infants from the Edmonton, Vancouver and Winnipeg sites of the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort was used. Metagenomic shotgun sequencing in a sub-set of samples was applied to study gut microbial pathways according to maternal pre-pregnancy weight status. Further, microbial metabolites (such as short chain fatty acids and other intermediate metabolites) were quantified by nuclear magnetic resonance (NMR) in fecal samples collected at 3-4 months of age. Measures of the mother's anthropometry pre-pregnancy and infant diet were obtained from standardized questionnaires and hospital records. Differences in fecal bacterial metabolites according to maternal pre-pregnancy overweight were detected by Mann-Whitney test. Results: Metagenomic analyses revealed that microbial pathways of carbohydrate degradation, pyruvate fermentation, and fatty acid metabolism were enriched in infants following maternal pre-pregnancy overweight compared to normal weight. Indeed, concentrations of pyruvate (intermediate energy metabolite; p=0.007) were lower in infants following pregnancy overweight, whereas those for valerate (short chain fatty acid; p=0.01) were higher. A lowering of pyruvate concentrations in infants after pre-pregnancy overweight was also detected in comparisons restricted to vaginally-delivered exclusively breastfed infants (median 0.2 vs 0.3, p=0.04, mmol/L), indicating independence from effects of mode of delivery and infant diet. Conclusions: Taken together, our preliminary metagenomic and metabolomic results show differences in microbial pathways according to maternal pre-pregnancy overweight status. Observations of lowered fecal pyruvate concentrations in infants of overweight mothers were consistent with elevated pyruvate fermentation.
Funded By: CIHR

women & children's health research institute

Abstract #: 59
Presenter: Brittany Matenchuk
Supervisor: Margie Davenport
Title: Physical Activity, Sedentary Behaviour and Cardiovagal Baroreflex Gain During Pregnancy
Authors: Brittany Matenchuk, Charlotte Usselman, Rshmi Khurana, Radha Chari, Maureen Devolin, Michael Stickland, Sandra Davidge, Craig Steinback, Margie Davenport
Affiliations: University of Alberta
Research Activity: Cardiovascular Health during Pregnancy
Investigation Type: Quantitative Research

Introduction
Autonomic control of heart rate is an important contributor to blood pressure regulation. Cardiovagal baroreflex gain (BRG) may be reduced during pregnancy, contributing to a higher incidence of hypotension. In other populations, BRG has been shown to positively correlate with physical activity levels.

Methods
We hypothesized healthy pregnant women (32.4±3.3 weeks gestation) meeting current guidelines for physical activity (>150 minutes per week) would have elevated BRG relative to those not meeting guidelines. Spontaneous BRG was calculated as the slope of the relationship between fluctuations in systolic blood pressure (SBP) and heart rate (HR) under baseline conditions (529±146 s) in 18 normotensive pregnant women (30±4 years, 27.4±4.1kg/m2). Moderate-vigorous physical activity (MVPA) and sedentary behaviour were assessed using accelerometry (6.6±1.0 days). Eight women met physical activity guidelines (ACT), while 10 did not (INACT).

Results
As expected, MVPA was higher in ACT (291.0±112.6min/week, 4.5±1.8% of daily activity) than INACT (74.3±44.4min/week, 1.3±0.7% of daily activity; P<0.001), while sedentary behaviour was not different between groups (69.2±7.0 vs 74.2±9.7% of daily activity; P=0.24). BRG was greater in ACT than INACT (HR: -3.5±1.5 vs -2.1±0.9 bpm/mmHg, P=0.02). Further, across all women, BRG was positively correlated with MVPA alone (HR: R= -0.725, P=0.001) and MVPA adjusted for sedentary behaviour (HR: R= -0.668, P=0.003).

Conclusion
These data suggest that MVPA modulates cardiovagal baroreflex gain in otherwise healthy pregnant women. These data suggest that physical activity during pregnancy may improve blood pressure regulation and that disparate findings of previous investigations regarding the effect of pregnancy on cardiovagal BRG might be explained by differences in physical activity levels between subject groups.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 60
Presenter: Amanda Paton
Supervisor: Dawn Kingston
Title: Assessment of healthcare providers' perinatal mental health education needs
Authors: Amanda Paton, Dawn Kingston, Lydia Vermeyden
Affiliations: University of Alberta
Research Activity: Women's Health : Mental Health
Investigation Type: Quantitative Research

Introduction: Perinatal mental health disorders are common in the perinatal period and have a significant impact on a woman, her child, and her family. Early intervention by healthcare providers (HCPs) may help to mitigate this impact through timely screening and treatment. Current HCP education on screening and assessment is limited and inconsistently offered. **Purpose**: The purpose of this cross-sectional survey study was to understand current HCP education needs are in the area of perinatal mental health (PMH). The research questions guiding the project were: (1) What are HCP perceived competencies in PMH? (2) What are HCP views and attitudes in PMH? (3) What factors (i.e. demographics and education) influence HCP competence and views/attitudes? **Methods**: Sample recruitment occurred via three online list-servs from February 3, 2015 to May 1, 2015 with a response rate of 34% (n=137). We generated descriptive statistics (%, N, mean/SD) for Q1 and Q2 and logistical regression models to identify factors associated with HCP competence and views. **Results**: Over three quarters (77.6%) of respondents were nurses, and 22.6% were family physicians. The mean age of respondents was 42±10.5. There was higher perceived knowledge and reported rate of assessment for the postpartum period (compared to the prenatal period). Approximately half of HCPs displayed adequate levels of comfort in assessment and screening. Having undergraduate/postgraduate or continuing education were significantly associated with increased levels of comfort.
Additionally, 3/9 attitudes assessed were not in line with best practice. **Conclusion**: These results highlight the need for provider education on mental health screening/assessment in order to increase HCP comfort, knowledge, and skills.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 61
Presenter: Maira Quintanilha
Supervisor: Maria Mayan
Title: Experiences of healthcare and service providers supporting pregnant and postpartum women living with poverty in rural areas in Alberta
Authors: Maira Quintanilha, Maria J Mayan, Jessica Thompson, Rhonda C Bell
Affiliations: University of Alberta
Research Activity: Maternal Research : Nutrution
Investigation Type: Qualitative Research

Introduction: In Canada, poverty and living rurally represent determinants of health that can negatively shape women's maternity care experiences including challenges accessing high quality, confidential and culturally sensitive maternity services. Pregnant and postpartum women living with poverty in rural areas in Alberta can access additional health and social support from community-based programs (CBPs) that are funded by federal and provincial health systems, as well as community agencies. These programs allow healthcare and service providers (e.g., nurses, dietitians, outreach workers) to promote mental health throughout pregnancy and postpartum, and healthy weights for both women and infants. This project sought to explore how healthcare and service providers support rural Alberta women living with poverty in the context of CBPs, and facilitators and barriers they experience in their roles.

Methods: A community-based participatory research approach was used to engage healthcare and service providers who work within a CBP; the CBP works with pregnant and postpartum women living with poverty in rural areas in Alberta. Focused ethnography was the method used, and involved 8 one-on-one interviews with providers and observations of CBP activities. All generated data were analyzed using qualitative content analysis to inductively derive codes and categories.

Results: Healthcare and service providers described that they commonly supported women through delivery of CBP activities and services, navigation to other supports, and crisis management (i.e., housing issues, addictions, family abuse). While the main focus of programming was to decrease food insecurity, it also created opportunities for providers to offer women emotional support, which was a pivotal aspect of the CBP. Having extensive experience working in their roles, knowing what services and supports are available in rural communities, and working well as a team facilitated providers' work within the CBP. In contrast, inconsistent leadership and funding in the last few years, and organizational discrepancies between rural communities represented significant barriers to their work.

Conclusion: CBP, healthcare and service providers can play a critical role in promoting mental health and healthy weights among women who are coping with various life adversities while pregnant and postpartum by offering them additional, much needed social and health supports. The role of CBPs and providers in women's perinatal health can be strengthened through strong leadership and clear organizational mandate. Most importantly, policies that support CBPs and providers in rural areas, and ensure adequate funding, will enable improved services to rural women during pregnancy and postpartum.

Funded By: Trainee Travel Grant

Abstract #: 62
Presenter: Sydney Schmidt
Supervisor: Margie Davenport
Title: Efferent muscle sympathetic nerve activity in normotensive pregnant women increases with gestational age
Authors: Sydney Schmidt, Charlotte Usselman, Margie Davenport, Craig Steinback
Affiliations: University of Alberta
Research Activity: Women's Health: Cardiovascular Regulation
Investigation Type: Quantitative Research

Introduction: Pregnancy is a state of increased sympathetic activity. Augmented activity is evident within the first trimester and there appears to be a further increase in activity from second to third trimesters. However, it is unclear if sympathetic activity stabilizes within the 3rd trimester and only a few studies have longitudinally assessed sympathetic activity during pregnancy. We hypothesized that there would be a progressive increase in sympathetic activity during late pregnancy.

Methods: A cross-sectional analysis of resting integrated muscle sympathetic activity (microneurography), blood pressure (Finometer) and heart rate (ECG) was conducted between 7 early 3rd Trimester (29 ± 2 wk gestation, 30 ± 4 yr, prepregnancy BMI: 22 ± 2 kg/m^2) and 8 late 3rd Trimester participants (38 ± 2 wk gestation, 32 ± 4 yr, prepregnancy BMI: 24 ± 2 kg/m^2). All participants were Caucasian, and 1 woman was longitudinally followed from pre-pregnancy to late pregnancy.

Results: Sympathetic burst frequency (32 ± 8 vs. 42 ± 9 bursts/min, $P < 0.05$) was significantly higher in late 3rd Trimester group. Though there were no significant differences in mean heart rates between the groups (83 ± 9 vs. 85 ± 10 heart beats/min, $P > 0.05$), the mean arterial pressure was lower in the early 3rd Trimester group (83 ± 7 vs. 92 ± 9 mmHG, $P = 0.07$), as was diastolic blood pressure (67 ± 6 vs. 76 ± 9 mmHG, $P < 0.05$). In the longitudinal case, sympathetic activity increased progressively with gestation, including within the 3rd trimester. These data suggests that SNA continues to increase throughout gestation despite the increase in blood pressure.

Conclusions: As gestation progresses, burst frequency increases, indicating higher levels of sympathetic activity. Though many studies have noted elevated sympathetic activity in late- relative to early-pregnancy, our study has shown that sympathetic activity does not stabilize within the trimester, and continues to increase throughout the 3rd trimester. The increase and stabilization of heart rate and blood pressure from early 3rd to late 3rd trimester, suggests that sympathetic activity may be driving hemodynamic factors to return to pre-pregnant levels at the end of gestation. More longitudinal case studies are needed to further explore these changes.

Funding: This study was funded by WCHRI, NSERC, and University of Alberta Human Performance Scholarship Fund.

Funded By: Partnership resources

women & children's health research institute

Abstract #: 63
Presenter: Kayla-Marie Smith
Supervisor: Vivian Huang
Title: An online educational portal is effective in improving knowledge regarding reproduction and IBD
Authors: Kelsey Wiestra, Kayla-Marie Smith, Lindsy Ambrosio, Leo Dieleman, Brendan Halloran, Karen Kroeker, Richard Fedorak, Keri-Ann Berga, Vivian Huang
Affiliations: University of Alberta
Research Activity: Maternal Health: Knowledge translation, pregnancy and IBD
Investigation Type: Qualitative Research

Introduction: Inflammatory Bowel Disease (IBD) is a chronic disease involving inflammation of the gastrointestinal tract. IBD affects patients through their adolescent and young adult years. Many IBD patients have a lack of knowledge regarding their disease and reproduction. The aim was to evaluate an online educational portal in improving knowledge regarding reproduction and IBD among IBD patients.

Methods: An online educational portal covering the topics of IBD and fertility, pregnancy, delivery, and breast feeding was developed by the University of Alberta IBD group. IBD patients (age 18 to 45yrs) were invited to participate in this study through clinic and advertisements (paper and social media).
Participants were randomized into two groups: (1) text-only webpages and (2) interactive modules (short videos, slide sets, self-quizzes, FAQ), and then given two months to access the online educational portal. Participants completed pre- and post- study Crohn's and Colitis Pregnancy Knowledge (CCPKnow) questionnaires to assess their pregnancy-related IBD knowledge. Responses were grouped as: poor (0 to 7), adequate (8 to 10), good (11 to 13) or very good (14 to 17). Pre and post CCPKnow scores were compared using non-parametric tests.

Results: As of August 1, 2015, 16 of 32 registered participants have completed the study (14 females and 2 males). Knowledge scores improved from pre-study CCPKnow 9.0 (IQR: 5.0-12.0) points to post-study 16.0 (IQR: 15.0-16.0) points (p value <0.01). Participants in the interactive group improved their CCPKnow scores by 2.0 more points than the text-only group, 7.5 (IQR: 3.3 - 11.0) points vs 5.5 (IQR: 4.3-8.3) points, respectively.

Conclusion: Access to an online educational portal improves knowledge regarding reproduction and IBD. Interactive modules improve knowledge more than text-only webpages.

Funded By: AIHS

women & children's health research institute

Abstract #: 64
Presenter: Andrew Woodman
Supervisor: Stephane Bourque
Title: Consequences of maternal iron-deficiency: fetal anemia, and hypoxia in select tissues of the conceptus
Authors: Andrew Woodman, Yael Mansour, Stephane Bourque
Affiliations: University of Alberta
Research Activity: Maternal Research : Fetal Origins of Adult Disease
Investigation Type: Quantitative Research

Introduction:

Iron deficiency (ID) affects populations across the socio-economic spectrum, making it the most prevalent nutritional deficiency worldwide. The incidence of ID anemia in pregnant women is of chief concern, with rates as high as 80 % in developing countries, and a prevalence of 17 % in Canada. Maternal ID during pregnancy has been shown to impact fetal iron status as well as growth trajectories of the developing conceptus, although the precise mechanisms underlying this intrauterine growth restriction are unknown. We hypothesize that maternal ID causes fetal anemia leading to hypoxia, which may be responsible for persistent maladaptive cardiovascular function after birth.

Methods:

Female rats were fed iron restricted diets throughout pregnancy; maternal and fetal hemoglobin (Hb) levels and body weights were assessed at gestational day (GD)21. Tissue immunofluorescence was carried out on GD21 pup tissues with fluorescent probes after dams were treated with pimonidazole to stain for hypoxia (<10 mmHg O_2).

Results:

Hb levels for pups from ID dams (3.36 ± 0.60 g/dL) were reduced compared to controls (9.21 ±0.73 g/dL, $P<0.001$), resulting in a 37% growth restriction ($P<0.001$). Maternal ID caused increased staining in fetal livers (median 0.058 a.u.) and kidneys (median 0.091 a.u.) versus controls (liver median 0.0 a.u., $P=0.19$ for n=3; kidney median 0.0 a.u., $P=0.06$ for n=5) which is indicative of hypoxia, while no differences in mean fluorescent intensity were observed in brains (ID median 0.0 a.u., control median 0.0 a.u., $P=0.33$ for n=5) or placentae (ID median 0.0 a.u., control median 0.0 a.u., $P=0.39$ for n=5).

Conclusions:

These findings suggest that compensatory mechanisms play a large role in maintaining oxygen delivery to the developing brain. Elucidation of the mechanisms through which neonates adapt to ID will allow for treatments targeting persistent adverse growth adaptations of the neonate.

Funded By: Start-up or Retention Funding

women & children's health research institute

Abstract #: 65
Presenter: Steffany Charles
Supervisor: Andrew S. Mackie
Title: Teens with congenital heart disease in transition from pediatric to adult care: Qualitative evaluation of a nurse-led intervention
Authors: Steffany Charles, Gwen Rempel , Laura G. Rogers, Kathryn Rankin, Elina Williams , Michelle Schuh, Dimi Dragieva, Sonila Mustafa, Andrew S. Mackie
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Qualitative Research

Introduction

Adolescent survivors of congenital heart disease (CHD) require lifelong specialized health care. Effective transition programs from pediatric to adult-care are warranted, but outcome data on transition programs remain limited. We sought to determine the effectiveness of a nurse-led intervention to prepare adolescents with CHD to successfully make this transition. This presentation describes findings of qualitative data from a clinical trial with 16-17 year olds at two centres.

Methods

Adolescents aged 16-17 years with moderate or complex CHD were randomized to a two-session transition intervention or usual care. The two-session intervention was conducted by one of five registered nurses in Edmonton and Toronto. Session 1 (1 hour) emphasized patient education and included nurse-led teaching, creation of a MyHealth Passport and goal setting. Session 2 (1.5 hours) was scheduled two months after Session 1 and emphasized self-management. It included a follow-up on goal setting, viewing videos on doctor-patient interactions and structured role-play scenarios. Qualitative data extracted from intervention logs, field notes and audio recordings of the sessions were analyzed through content and thematic analysis and managed using NVivo 10.

Results

Data from 111 sessions with 57 adolescents were analyzed. Creation of the MyHealth Passport, patient goal setting and the role-plays were the important sequential steps for the participants. Analysis of participants in the intervention group revealed 4 categories: 1) the independent adolescent who was already managing aspects of their own care (5%); 2) the adolescent who was now ready for transition after completing both intervention sessions (46%); 3) the “at risk” adolescent who warranted immediate follow-up (14%). These adolescents engaged in risky behaviours and appeared uninterested in learning how to manage their own health; and, 4) the adolescent who was still in need of extra coaching (26%). After completing both sessions, this group still did not have a good understanding of their heart condition, struggled with setting their own goals and lacked confidence in the role-play scenarios. Nine percent of adolescents could not be classified based on the qualitative data available.

Conclusions

Qualitative analysis of extensive data generated in this clinical trial contributed to determining the most important components of the nurse-led sessions: creation of a MyHealth passport, goal-setting, and role-plays. This data will guide health-care professionals to optimize an individualized approach for ensuring transition readiness for adolescents and young adults with CHD.

Funded By:

women & children's health research institute

Abstract #: 66
Presenter: Won Shik Choi
Supervisor: Lesley Mitchell
Title: The A1298C polymorphism in the methylenetetrahydrofolate reductase gene is a risk factor for deep vein thrombosis in pediatric cancer patients.
Authors: Won Shik Choi, Kevin Dietrich, Maria Spavor, Sara Israels, Jackie Halton, Evan Shereck, Lesley Mitchell
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Oncology
Investigation Type: Quantitative Research

Introduction: One third of pediatric cancer patients will develop a deep vein thrombosis (DVT) during their cancer treatment. The occurrence of DVT is associated with significant morbidity and mortality. As not all children will develop DVT, determining biomarkers that indicate which children are at risk is important in order to optimize clinical care. Elevated plasma homocysteine levels are a risk factor for DVT in adults. Two single nucleotide polymorphisms (SNPs) in the MTHFR gene have been demonstrated to cause an elevation in plasma levels of homocysteine. The objective of the study was to determine the association of DVT with genetic polymorphisms in the MTHFR gene in pediatric oncology patients.

Methods: We performed a multicenter cross-Canada case control study. Survivors of childhood cancer who experienced DVT while undergoing cancer treatment
(cases) were matched with survivors of childhood cancer who did not experience DVT (controls). We recruited 369 patients (109 patients with DVT and 260
controls without DVT) and 104 normal controls. An r^2 of 0.8 for linkage disequilibrium and a MAF > 5% were used as threshold values for SNP selection. We
identified 8 tagging SNPs including rs1801131: A1298C and rs1801133: C677T. Analysis of genetic polymorphisms was done by allele specific primer extension.

Results:Frequencies of the 1298CC genotype were 13.7% in patients with DVT as compared to 7.1% in patients without DVT (OR=2.09; 95% CI:0.99-4.4, P=0.052). The frequency of the 1298CC genotype between the normal controls and all cancer patients was similar (OR=1.07; 95% CI:0.49-2.34, P=0.853).

Conclusions: We have identified an association between DVT and A1298C polymorphism in childhood cancer patients.

Acknowledgments: WSC is supported by AIHS summer student award and the study was funded by the Hair Massacure Foundation

and CIHR. Funded By: AIHS

women & children's health research institute

Abstract #: 67
Presenter: Ian Robertson
Supervisor: Jason Dyck
Title: Exposure of juvenile mice to doxorubicin impairs compensatory cardiac hypertrophy in adult-onset hypertension
Authors: Ian Robertson, Beshay Zordoky, Nobutoshi Matsumura, Shereen Hamza, Darryl Mah, Carrie Soltys, Grant Masson, Donna Beker, Jason Dyck
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction: Over the past 40 years, advancements in the diagnosis and treatment of cancer have increased survival rates in children diagnosed with cancer. Anthracyclines, such as doxorubicin (DOX), are among the most effective chemotherapeutics used in the treatment of cancer. However, the clinical utility of DOX is offset by its well-known dose-dependent cardiotoxicity, which often does not appear until many years following the initial cancer treatment. Indeed, despite improved cancer survival rates, children treated with DOX have an increased likelihood of developing cardiomyopathy in adulthood. Unfortunately, little is known about the mechanism behind this delayed cardiomyopathy; therefore, we developed an animal model that recapitulated the clinical manifestation of DOX-induced late-onset cardiotoxicity. Moreover, since a higher incidence of hypertension has been observed in cancer-survivors treated with DOX, we investigated whether juvenile DOX exposure impaired the ability of the mice to adapt to angiotensin II (ANG)-induced hypertension.

Methods: Juvenile mice were given an intraperitoneal injection of DOX or an equal volume of saline once a week for three weeks (cumulative DOX dose of 12 mg/kg) and then monitored for an additional 5 weeks. This treatment regimen did not cause any mortality or significant morbidity. Following the recovery period, mice were infused with a low or high dose of ANG or saline for an additional 2-weeks. Echocardiography was used to measure cardiac structure and function, and blood pressure was monitored using tail cuff and telemetry.

Results: Following the 5-week recovery period from saline/DOX administration, there was no cardiac hypertrophy and no difference in cardiac function between the two treatment groups. Interestingly, after ANG treatment, all the saline-injected mice tolerated the higher dose of ANG, yet the DOX-treated mice were much more vulnerable, with only 33% surviving the full 2-week treatment. All the mice survived the full 2-week treatment with the lower ANG dose, and were therefore studied further. ANG induced an increase in blood pressure in both DOX- and saline-treated mice; however, only the saline-treated mice experienced the concomitant increase in myocardial hypertrophy. This indicates that the hearts of the DOX-treated mice are unable to adapt to hypertension.

Conclusion: We have developed a mouse model of DOX-induced cardiotoxicity that demonstrates that DOX treatment early in life impairs the ability of the adult heart to adapt to pathological stress such as hypertension. This mouse model will allow us to characterize the molecular mechanism behind late-onset DOX cardiotoxicity and investigate potential pharmacological interventions to prevent this.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 68
Presenter: Lindsay Ryerson
Supervisor:
Title: Two year prospective single center review of heparin anticoagulation in extracorporeal life support
Authors: Lindsay Ryerson, Mary Bauman, Gonzalo Garcia Guerra, Don Granoski, Aisha Bruce, Patti Massicote, Laurance Lequier
Affiliations: University of Alberta
Research Activity: Pediatric critical care
Investigation Type: Quantitative Research

Introduction: Anticoagulation is an imperfect science which is made more complicated by extracorporeal life support (ECLS). A continuous unfractionated heparin (UFH) infusion is the most common anticoagulant used in ECLS. The optimal method to measure UFH efficacy on ECLS is unknown. Bleeding and thrombotic complications, as defined by ELSO, are common and are associated with decreased survival. Our objective was to prospectively evaluate our UFH dose and monitoring of UFH anticoagulation as well as patient bleeding, patient thromboses and circuit interventions.

Methods: Prospective review of ECLS anticoagulation at Stollery Children's Hospital from May 2013 to May 2015. All neonatal and pediatric patients on VA and VV ECLS that provided written informed consent were included. The primary outcome was patient bleeding. Major bleeding was defined as bleeding that was retroperitoneal, pulmonary or involved the central nervous system; bleeding more than 20ml/kg over 24 hours or bleeding that required surgical intervention. Minor bleeding was defined as bleeding more than 10ml/kg over 24 hours. Secondary outcomes included patient thrombosis and circuit intervention. Significant patient thrombosis was defined as intracranial, pulmonary, renal, gastrointestinal or splenic infarct. A circuit intervention was defined as the need to change the entire circuit, oxygenator, centrifugal pump or any other individual circuit component.

Results: 62 ECLS runs in 56 children were included. Median age was 1.48 months (IQR 0.47-8.9) and mean weight was 7.55 kg (SD 11.5). 56 (90%) runs were VA ECLS and 6 runs were VV ECLS. 46 runs (74%) were in cardiac patients. Indication for ECLS was sepsis in 6%, failure to wean from cardiopulmonary bypass in 11%, hypoxemia in 21%, low cardiac output syndrome in 24% and ECPR in 37%. Median UFH dose was 28 U/kg/hr (IQR 22-36). Median ACT was 155 (IQR 143-165).
Median anti-Xa was 0.42 U/ml (IQR 0.31-0.51) and median aPTT 91 (IAR 69-120). 21% of the runs were complicated by major bleeding; 3% had minor bleeding. Two patients had significant patient thromboses. At least one circuit intervention was performed in 40% of the runs. 41 patients (76%) survived to hospital discharge. There was no association between major bleeding or need for circuit intervention with survival to hospital discharge.

Conclusions: Bleeding, as defined in our study, is less common than previously reported and is not associated with mortality. Circuit interventions are common, but are not associated with worse outcomes.

Funded By: ELSO

women & children's health research institute

Abstract #: 69
Presenter: Morgan Sosniuk
Supervisor: Lori West
Title: Differentiation of B cells into carbohydrate-specific IgM-secreting cells via B cell receptor stimulation
Authors: Morgan Sosniuk, Esmé Dijke, Lori West
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Transplant
Investigation Type: Quantitative Research

Introduction: Transplantation is a lifesaving therapy for patients with end stage organ failure or chronic illness. A major obstacle to providing this therapy effectively is insufficient donor organs or tissues. Usage of blood-group ABO-incompatible (ABOi) organs, or tissues from pigs such as neonatal porcine islets (NPIs) (xenotransplantation) could expand the donor pool and reduce wait list times. However, natural antibody production to carbohydrate antigens, such as ABO antigens and the xenoantigen alpha-gal, form an immunological barrier. B-cell ELISPOT assays can be used to quantify the number of carbohydrate-specific antibody-secreting cells (ASCs) and to study mechanisms that may modulate these cells. In our current protocol, B cells are stimulated through a T-independent pathway by Toll-like receptor (TLR) 9 stimulation with CpG. Here, we studied whether B cells can differentiate into carbohydrate-specific ASCs through B cell receptor (BCR) stimulation with or without T-cell help.

Methods: Peripheral blood mononuclear cells (PBMCs), isolated B cells, or B cells co-cultured with T cells were stimulated in the presence of IL-2, IL-10, IL-15 and BAFF with CpG, anti-IgM antibodies, or irradiated NPIs. After seven days, ELISPOT assays were performed to quantify the number of total, anti-alpha-gal or anti- ABO IgM ASCs.

Results: Anti-IgM stimulation of only B cells resulted in fewer total IgM ASCs compared to CpG stimulation (0 – 214 vs. 20 – 624 ASCs/10,000 cells, respectively (n=5)), albeit not significantly. The presence of T cells and/or other mononuclear cells had no significant effect on the number of IgM ASCs after anti-IgM or CpG stimulation (n=3). Furthermore, the number of anti-alpha-Gal IgM ASCs was lower after anti-IgM stimulation than after CpG stimulation of all cell cultures (B cells only: 0-1 vs. 0-17 ASCs/10,000 cells (n=4); PBMCs: 0 vs. 1-3 ASCs/10,000 cells (n=3); B + T cells: 0-1 vs. 1-15 ASCs/10,000 cells (n=3), respectively). The same trend was observed for non-self anti-ABO IgM ASCs (n=2). Total IgM ASCs and anti-alpha-Gal IgM ASCs after NPI stimulation were detected in one of two experiments (125 IgM ASCs/10,000 cells and 11 anti-alpha-Gal IgM ASCs/10,000 cells).

Conclusion: B cells can be differentiated into carbohydrate-specific IgM ASCs via BCR stimulation with anti-IgM antibodies or NPIs. However, since these stimulations result in fewer ASCs than CpG stimulation, stimulation through the BCR may be less effective than stimulation through TLR-9 to differentiate B cells into IgM ASCs *in vitro*. Future experiments will include the use of cross-linking to further enhance stimulation through the BCR.

Funded By: Alberta Innovates Health Solutions

women & children's health research institute

Abstract #: 70
Presenter: Justin Elliott
Supervisor: Oana Caluseriu
Title: Antisense therapy in cell lines derived from patients with fibrodysplasia ossificans progressiva (FOP)
Authors: Justin Elliott, Punit Virk, Yusuke Echigoya, Rika Maruyama, Toshifumi Yokota, Oana Caluseriu
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Introduction: Fibrodysplasia ossificans progressiva (FOP) is a rare, autosomal dominant genetic disease characterized by progressive heterotopic ossification which results in impaired joint motion, severely impacted quality of life, and decreased lifespan. The causative mutation in almost all cases of FOP is a single gain-of-function missense mutation (R206H) in the *ALK2* gene, which encodes for a bone morphogenetic protein (BMP) receptor. In FOP patients, the mutant ALK2 receptor protein is constitutively signalling in a ligand-independent manner and promotes osteogenic conditions in maladaptive locations of the body. Current treatments for FOP are only mildly supportive. A potential novel therapy for FOP would effectively decrease levels of the mutant gain-of-function ALK2 receptor, modulating downstream pSmad1/5 signalling and reducing ectopic bone formation. This project aims to evaluate the use of modern antisense oligonucleotides (AONs) for downregulation of *ALK2* expression in FOP cells.

Methods: Locked Nucleic Acid (LNA)-DNA chimera gapmers (a modern AON technology) were selected with sequences to specifically target various segments of the *ALK2* mRNA and induce RNase H-mediated cleavage of this transcript to reduce *ALK2* expression. Fibroblast cell culture lines derived from FOP patients are treated with BMP4 to potentiate the ALK2 – pSmad signalling pathway, and are then transfected with the LNA-DNA gapmers. Resulting changes in *ALK2* gene expression or osteogenic pSmad1/5 signalling is determined using Semi-Quantitative Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) to measure relative mRNA transcript levels as well as Western Blotting to quantify target protein levels.

Results: Evaluation of LNA-DNA gapmer AON-treated cells by RT-PCR, has demonstrated reduction of *ALK2* expression by up to 85% at the mRNA level. Quantification of protein levels by Western blotting has also confirmed that AONs can reduce the amount of the ALK2 receptor protein by up to 40%. Furthermore, Western blotting to quantify the activation of the downstream signalling protein Smad1/5, has shown that the otherwise pathogenic constitutive ALK2 signalling in FOP cells can be reduced to normal healthy levels and beyond with AON treatment.

Conclusion: Our current study shows that antisense therapies, utilizing LNA-DNA gapmers to reduce expression of the pathogenic *ALK2* gene, can be effective at restoring healthy levels of osteogenic signalling in a cell culture model of Fibrodysplasia Ossificans Progressiva (FOP).

Funded By: University Hospital Foundation

Abstract #: 71
Presenter: Maram Hulbah
Supervisor: Gregory Tyrrell
Title: Identification of a gene in Group B Streptococcus (GBS) involved in the surface expression of GBS- phosphoglycerate kinase.
Authors: Maram Hulbah
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Title:

Identification of a gene in Group B Streptococcus (GBS) involved in the surface expression of GBS- phosphoglycerate kinase.

Authors:

Maram J. Hulbah and Gregory J. Tyrrell

Introduction (Purpose):

Phosphoglycerate kinase (PGK), a glycolytic enzyme, is an anchorless surface protein on Group B Streptococcus (GBS) and has been identified to bind important mammalian proteins, including plasminogen. The mechanism by how this protein is secreted or becomes surface associated is unknown. This study identified a gene, *sag912,* in GBS that has a role in the surface expression of PGK.

Material and Methods:

SDS-PAGE and Far Western Blots (FWB) were used to identify the protein band from fractionated GBS with whole cell lysate (WCL), following probing with recombinant GBS-PGK and anti-GBS-PGK antibody. The identity of the protein band was determined by Mass Spectrometry (MS). GBS *sag912::erm* mutant was created by inserting an erythromycin resistance cassette into *sag912*. The expression of GBS-PGK on the surface of GBS *sag912::erm* mutant was investigated by ELISA. The antiphagocytic ability of GBS and GBS *sag912::erm* mutant strains was determined by measuring their abilities to multiply in fresh human blood during a three hour incubation period.

Results:

Antibody against GBS-PGK reacted with proteins of molecular mass of 15 and 43 KDa in whole cell lysate and cell wall fractions. MS analysis confirmed the identity of the protein at 15 KDa as Sag912, a hypothetical protein with molecular mass of 43 KDa. This protein is predicted to be a polysaccharide binding protein. The surface expression of GBS-PGK was reduced in GBS *sag912::erm* mutant compared to the parent strain. The mutant was found to display phenotypic changes which included decreased hemolytic activity and reduced CAMP factor activity on blood agar. In addition, the antiphagocytic activity of the mutant strain was inhibited by 98% compared to the parent strain.

Conclusions:

These results suggest that *sag912* regulates the expression of PGK on the surface of GBS and other GBS virulence determinants and is therefore likely to play an important role in GBS pathogenesis.

Funded By: Ministry of higher education of Saudi Arabia

Abstract #: 72
Presenter: Christen Klinger
Supervisor: Joel Dacks
Title: Phylogenetic analyses reveal novel membrane trafficking factors in apicomplexan parasites
Authors: Christen Klinger, Joel Dacks
Affiliations: University of Alberta
Research Activity: Women and Children's Health: Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction

Apicomplexa are unicellular parasites important on a global scale, including the causative agents of cerebral malaria *Plasmodium falciparum* and congenital toxoplasmosis *Toxoplasma gondii.* Apicomplexa are obligate intracellular parasites; treatments that block host cell invasion lead to parasite death *in vitro* and decreased pathogenecity *in vivo.* Hence, invasion represents a key point, not only in the parasite life cycle, but also for intervention. Invasion relies, in part, on specialized secretory organelles micronemes and rhoptries, colloquially known as "invasion organelles". We, as well as others, have hypothesized that these invasion organelles are derived late endocytic compartments, and hence their biogenesis and maintenance should rely on the machinery of the membrane trafficking system (MTS). However, invasion organelles exist in the presence of canonical endocytic compartments, suggesting that the advent of new MTS machinery, and/or neofunctionalization of existing machinery, should facilitate their upkeep; studies to date have shown loss of MTS machinery with no observed gains. Hence, the relationship between the MTS and pathogenesis remains unclear. This is due, in part, to the lack of a suitable outgroup to understand the evolutionary transition from a free-living to pathogenic state. Such an outgroup was described recently: the chromerid algae *Chromera velia* and *Vitrella brassicaformis.*

Methods

We have used pairwise and Hidden Markov Model (HMM)-based homology search methods to identify all known membrane trafficking factors in 32 genomes, including the chromerid algae and 20 apicomplexan species. Identified sequences were subjected to in depth maximum-likelihood and Bayesian phylogenetic analyses.

Results

The majority of gene families analyzed showed previously observed patterns, namely the lineage-specific loss of trafficking factors. However, analysis of MTS machinery forming large paralogous families, including the Ras from brain (Rab), ADP-ribosylation factor (Arf), and Tre-2/Bub2/Cdc16 (TBC) families, has revealed the presence of paralogues that form phylogenetic clades distinct from those in other closely related organisms. These novel clades can be further subdivided into those comprised of sequences from Apicomplexa only, Apicomplexa and chromerids, or the latter subset together with other closely related algae.

Conclusions

We have identified novel membrane trafficking factors in diverse apicomplexan parasites. We expect downstream characterization of each of these clades to reveal functions including, but not limited to, novel pathogenic factors and those involved in pathogenesis that are adapted from alternate ancestral functions. These studies will provide insight into the process of invasion organelle biogenesis and shed light on the evolutionary transition from free-living algae to deadly intracellular parasites.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 73
Presenter: Dory Sample
Supervisor: Hoon Sunwoo
Title: Safety, symptoms, and lab measures in an anti-gluten IgY antibody (AGY) trial for Celiac Disease
Authors: Dory Sample, Levinus Dieleman, Hien Huynh, Heather Rylance, Cheri Robert, Rick Watts, Sung Kang, Biwen Xu, Hoon Sunwoo
Affiliations: University of Alberta
Research Activity: women and children health
Investigation Type: Quantitative Research

Introduction

Approximately 1% of the worldwide population has celiac disease (CD), a permanent intolerance to ingested gluten in genetically susceptible individuals. The disease affects more females than males (~3:1), and the rate is increasing, particularly for children. The gluten free diet (GFD) is the only current treatment and non-adherence is associated with significant morbidity and mortality. However, compliance is difficult as food labeling can be vague and gluten containing products are widespread. Cross contamination during food preparation is a constant risk, and many individuals with CD avoid eating outside the home for this reason, adversely affecting quality of life. Additionally, many individuals with CD experience ongoing symptoms, despite dedication to a GFD. Additional treatment options are clearly needed. Anti-gluten IgY antibody (AGY) is a novel treatment using an oral egg yolk based antibody to neutralize the toxic effects of gluten, and may offer a safe and effective treatment option for CD.

Methods

This first-in-man, 6-week, open-label, single arm pilot safety study was conducted in a hospital ambulatory care clinic, in adults with biopsy proven CD who follow a GFD but still have periodic symptoms. The primary outcome was safety, measured by adverse events and laboratory tests. A run-in period of 2 weeks determined compliance with questionnaires, including the Celiac Symptom Index (CSI), and evaluation of baseline safety laboratory results. This was followed by a 4-week treatment period with 2 x 500mg capsules AGY, taken just prior to each meal. Adverse events were recorded from the time of consent to study end. Daily CSI assessment, periodic laboratory measures, Health Related Quality of life (HRQoL), anti-tissue transglutaminase and anti-gliadin IgA/IgG, as well as lactulose mannitol excretion ratio (LMER) were measured.

Results

Eleven individuals enrolled, ten completed the study (9 female; mean age 43.4 years; all Caucasian). No safety concerns were identified. Most participants had fewer symptoms, and improved HRQoL, antibody levels, and LMER when taking AGY relative to the run-in period; some changes were statistically significant.

Conclusions

AGY is safe and may improve CD related outcome measures. A larger study powered for efficacy evaluation is

warranted. Funded By: Alberta Livestock and Meat Agency, IGY Inc and Vedanta Group Ltd

Abstract #: 74
Presenter: Yue Ting Kero Yuen
Supervisor: Linda Chui
Title: Characterization of Listeria monocytogenes Biofilm Formation
Authors: Yue Ting Kero Yuen, Linda Chui, Brendon Parsons
Affiliations: Other
Research Activity: Maternal Research : Infection, Inflammation, Immunology
Investigation Type: Mixed Methods

INTRODUCTION: *Listeria monocytogenes* is a food-borne pathogen that is prevalent in the environment. It can cause life-threatening listeriosis in pregnant women, newborns, elderly, and immunocompromised individuals. Many outbreaks are frequently linked to foods, due to *L. monocytogenes*'s ability to survive harsh living conditions such as food processing plants. Part of this bacteria's resiliency is attributed to its formation of biofilm. We hypothesized that the serotype, growth conditions, and environmental factors affect the biofilm formation of *L. monocytogenes.* METHODS: Bacterial serotypes included 1/2a, 1/2b, 1/2c, 3a, 3c, 4a, 4b, and 4e. Tryptic soy broth (TSB) diluted in saline was used as the growth media, and the lengths of incubation were 24, 48, or 72 hours. Temperatures of incubation included 4^{o} C, 22^{o} C, 30^{o} C, or 37 C and the initial cell counts were exponential increases between 10^{1} and 10^{7} cells. We used DrySan HS™, a sanitizing agent for disinfecting surfaces in meat-processing plants, to coat the surfaces on which *L. monocytogenes* was inoculated. Biofilm formed on the underside of PCR plates in these various conditions, was stained with 1% crystal violet, and quantified by spectrophotometry at 595nm. RESULTS: Preliminary results showed that regardless of serotype, gross biofilm formation generally peaked at 48 hours of incubation, with a low initial cell count (approximately 100 cells), and a low concentration of TSB (10%). Optimal growth temperatures were either 22^{o}C or 30^{o} C depending on serotype. Different serotypes expressed different gross amounts and patterns of biofilm formation. Pre-treatment of the culture surfaces in DrySan HS™ had a minimal effect on biofilm formation. CONCLUSIONS: Therefore, we determined the effects of certain environmental factors and growth conditions on *L. monocytogenes* biofilm formation, providing insight on its growth patterns and requirements.

Funded By:

women & children's health research institute

Abstract #: 75
Presenter: Rawad Lashhab
Supervisor: Emmanuelle Cordat
Title: Role of kAE1/Claudin-4 interaction in maintaining acid/base and electrolyte homeostasis
Authors: Rawad Lashhab, Alina Rumley, Ensaf Almomani
Affiliations: University of Alberta
Research Activity: Paediatric Nephrology
Investigation Type: Quantitative Research

Introduction

Distal renal tubular acidosis (dRTA) is a renal defect in acid secretion and, as a consequence, bicarbonate absorption in the distal nephron tubules. dRTA patients develop renal stones, hypokalemia, hyperchloremia, nephrocalcinosis, metabolic acidosis and defective urine acidification in addition to facing difficulties to thrive. In the recessive form, it affects infants at birth. Different mutations in genes encoding the anion exchanger 1 (AE1) can result in dRTA. AE1 is a transmembrane protein that is expressed in the kidney (kAE1), and functions as Cl^-/HCO_3^- exchanger. The kAE1 is expressed in the collecting ducts of the nephrons, more specifically in the a-intercalated cells (a-IC). Several mutations in the gene encoding the kAE1 can result in mistrafficking of the protein to the apical membrane or intracellular retention or dysfunctional protein at the basolateral membrane, in which it results in dRTA. A yeast two-hybrid assay, found that kAE1 interacts with Claudin-4 (Cldn-4). Cldn-4 is a tight junction protein with 4 transmembrane domains and 2 extracellular loops and it is expressed in many tissues including the intercalated cells in the collecting ducts of the nephrons. Cldn-4 interacts with another Cldn-4 from a different cell in trans interaction form, providing a paracellular Cl^- selective pore through the tight junction. Kidney-specific mouse Cldn-4 knockout result in hypotension, hyperchloremia, metabolic alkalosis, lethal hydronephrosis and urethelial hyperplasia. We hypothesized that kAE1/Cldn-4 interaction regulates pH and electrolyte homeostasis. Our aim is to confirm this interaction and to determine its role in the acid/base balance and electrolyte homeostasis.

Methods

In polarized renal epithelial cells expressing kAE1-wild type (kAE1-WT) protein, we performed immunofluorescence and Proximity Ligation Assays to show co-localization between kAE1 and Cldn-4 at the basolateral membrane. We confirmed this interaction by co-immunoprecipitations assay. We performed functional assay and Ussing chamber experiments to test the effect of kAE1 expression upon Cldn-4 function.

Results

Immunofluorescence and Proximity Ligation Assays showed a co-localization between kAE1 and Cldn-4 at the basolateral membrane. Immunoprecipitations confirmed the interaction between both proteins. Preliminary data from functional assay showed no significant difference in kAE1 function upon Cldn-4 expression. Ussing Chamber experiments revealed no significant change in transepithelial electrical resistance or paracellular Cl^- & Na^+ permeability upon kAE1 expression.

Conclusion

Our results confirm the interaction between kAE1 and Cldn-4, and further experiments will be needed to determine the role for this interaction in electrolyte homeostasis.

Funded By: Innovation Grant

Abstract #: 76
Presenter: AKM Shahid Ullah
Supervisor: Emmannuelle Cordat
Title: Does SLC26A7 compensate the absence of kidney anion exchanger 1 in distal renal tubular acidosis?
Authors: AKM Shahid Ullah, Carly Rumley, Velentina Peleh, Rawad Lashhab, Mattia Berrini
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Quantitative Research

Introduction

Tiny Tim in the Charles Dickens's "A Christmas Carol" portrays a child with small stature, malformed limbs and periods of weaknesses, who was possibly suffering from distal tubular acidosis (dRTA) as a result of poor HCO_3^- transport function in the kidney. Many other kids in Canada and across the globe are suffering from this disease due to the malfunction of the kidney anion exchanger (kAE1), which is expressed at the basolateral membrane in the collecting duct cells of the kidney. SLC26A7 is also a Cl^-/HCO_3^- exchanger protein at pH above 7.0 and acts as a HCO_3^- stimulated Cl^- channel at lower pH. In stimulated acid-secreting cells SLC26A7 switches its function from a Cl^- channel to a HCO_3^- transporter. This study aims to clarify the role of the protein SLC26A7 in renal epithelial cells relative to the kAE1 in physiological or pathological conditions. We hypothesized that SLC26A7 is unable to compensate for the loss of kAE1 in distal renal tubular acidosis (dRTA). The expression level, localization and function of SLC26A7 in control renal epithelial cells or cells expressing kAE1 wild type (WT) or cells carrying a dRTA mutation were tested.

Methods

Madin Darby canine kidney (MDCK) cells stably expressing combinations of myc, HA and Flag tagged plasmid constructions containing SLC26A7 and kAE1 were lysed, and protein contents were compared by immunoblot in control, hyper-osmotic or acidic conditions. Polarized cells were cultured on semi-permeable membrane for immunofluorescence and confocal microscopy. Bicarbonate transport assay was conducted using Photon Technologies International (PTI) fluorimeter to record BCECF (2', 7'-Bis-(2-Carboxyethyl)-5-(and-6)-Carboxyfluorescein, Acetoxymethyl Ester) fluorescence fluctuations in NaCl or Na-Gluconate buffers.

Results

Immunoblot experiments show that SLC26A7 is more abundant in hyper-osmotic conditions than in control conditions whereas kAE1 is stable. Immunoblot experiments with cycloheximide demonstrate that the up regulation of SLC26A7 expression is not due to a longer half-life in hyperosmotic condition. No significant difference in initial transport rate between kAE1 wt and SLC26A7 proteins in MDCK cells was found which supports that at physiological pH, both proteins behave as a Cl^-/HCO_3^- exchanger. Functional assay also showed an increase in the SLC26A7 function in presence of Na-gluconate than other hyperosmotic medium. However, acidic pH decreased the abundance of both SLC26A7 and kAE1.

Conclusion

Despite the expression of the Cl^-/HCO_3^- exchanger SLC26A7 in collecting duct cells, acidic environment in dRTA patients reduces expression of the protein, likely resulting in a lack of compensatory Cl^-/HCO_3^- exchange.

Funded By: Innovation Grant

Abstract #: 77
Presenter: Shane Wiebe
Supervisor: Todd Alexander
Title: The role of NHE8 in renal proximal tubule calcium reabsorption
Authors: Shane Wiebe, Todd Alexander
Affiliations: University of Alberta
Research Activity: Women and children's kidney and bone health
Investigation Type: Quantitative Research

Abnormalities in calcium homeostasis can result in osteoporosis and kidney stones, two childhood disorders with increasing prevalence. Improved therapies for these childhood disorders can only be achieved through increased fundamental knowledge about calcium handling. In the kidneys, filtered calcium (Ca^{2+}) is reabsorbed along the nephron. To delineate the renal regulation of calcium reabsorption, we performed a micro array on mRNA from mice treated with the calcium sensing receptor agonist cinacalcet. This revealed that the sodium/hydrogen exchanger isoform 8 (NHE8) mRNA expression was decreased. These results were confirmed by quantitative PCR. Further administration of vitamin D to mice also decreased NHE8 mRNA expression. In contrast, by semi- quantitative western blot analysis renal NHE8 protein expression was increased in the same mice treated with cinacalcet or vitamin D. We therefore hypothesized that NHE8, similar to NHE3, plays a role in calcium homeostasis by facilitating the reabsorption of filtered calcium. To this end, we are validating a renal cell culture model, normal rat kidney (NRK) cells. We confirmed apical surface expression of NHE8 in NRK cells using surface biotinylation and immunofluorescence techniques imaging the Z plane of the cells. Functional studies demonstrate EIPA inhibitable sodium/hydrogen exchanger activity. We are also knocking down NHE8 and repeating these studies. To delineate the molecular role of NHE8 in calcium homeostasis, we will use this model to measure paracellular and transcellular Ca^{2+} flux across confluent monolayers in the presence and absence of functional NHE8. Future studies will explore the calcium phenotype in the NHE8 knockout mouse.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 78
Presenter: Ashley Bahry
Supervisor: Jerome Yager
Title: Long term behavioral deficits associated with intrauterine growth restriction and the effect of prophylactic broccoli sprout supplementation
Authors: Ashley Bahry, Edward Armstrong, Jennifer Corrigan, Jerome Yager
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

Introduction: Intrauterine growth restriction (IUGR) resulting from placental insufficiency (PI) is a risk factor for many neurodevelopmental complications, including cerebral palsy. Currently, there are no preventative treatments to target these adverse events that occur during gestation. However, complimentary and alternative medicines may provide safe and effective treatment for the complications of PI. Our laboratory has shown that Broccoli sprouts (BrSp) reduces damage and prevents the developmental delay in a model of PI in the rat.

Objectives: To determine if BrSp supplementation during pregnancy and the pre-weaning can permanently prevent the long term neuro-pathological consequences of IUGR in the offspring of dams exposed to a model of PI.

Methods: Timed pregnant Long-Evans rats underwent either bilateral uterine artery ligation (BUAL) or sham surgery, on day 20 of a 23-day gestation. Rat dams treated with BrSp were fed 200 mg/day from gestational day 15 until the pups were weaned at 21 days. Two male and 2 female pups from each litter were grown to 6 weeks of age, when behavioral testing commenced. Neurological deficits were measured through tapered beam, open field, elevated plus maze, gait, water maze and single pellet behaviour tests. Neuropathology was assessed on day 80.

Results: BUAL surgery significantly reduced the weights of pups at birth ($p<0.001$), resulting in IUGR, which was not sustained into adulthood. IUGR animals made significantly more foot faults in the tapered beam test than sham animals ($p<0.001$), which was prevented in animals treated with BrSp ($p<0.01$). IUGR animals spent significantly more time in the closed arms of the elevated plus maze than sham ($p<0.001$). This effect was not seen when the animals were treated with BrSp. Male IUGR animals had a defective reaching strategy in the single pellet test ($p<0.01$), and an inefficient swim path in the water maze ($p<0.001$), also prevented after BrSp treatment (NS, $p<0.05$ respectively). No significant differences in myelination, ventricular or brain volume were found between IUGR and sham animals.

Conclusions: PI, resulting in IUGR causes deficits in motor and cognitive function in the adult rat. BrSp supplementation during pregnancy and lactation significantly decreases these behavioral deficits. This has strong implications for BrSp as a preventative treatment of neurological complications in IUGR offspring as a result of PI.

Funded By: Start-up or Retention Funding

women & children's health research institute

Abstract #: 79
Presenter: Ashley Bahry
Supervisor: Jerome Yager
Title: Effects of Dietary Broccoli Sprout Supplementation on Alterations in Brain Connectivity of Intrauterine Growth Restricted Offspring
Authors: Ashley MA Bahry, Edward A Armstrong, Jerome Yager
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Qualitative Research

Introduction: Placental insufficiency (PI) resulting in intrauterine growth restriction (IUGR) can lead to many neurological complications including learning disabilities and cerebral palsy. Preventative treatments to target these adverse events that occur during gestation, are currently unavailable. However, natural health products, such as broccoli sprouts (BrSp), may be a potential prophylactic treatment as we have previously shown BrSp to prevent developmental delays in a model of PI in the rat. Although abnormalities in both cognition and motor functioning are evident in these IUGR offspring, no overt pathology was present, long term. It is suggested that alterations in neuronal morphology and neurotransmitter signaling in these offspring may, therefore, be the underlying mechanism.

Objectives: 1) Determine if a model of PI in the rat causes detrimental effects to the serotonin (5-HT) and dopamine (D) pathways as well as neuronal morphology. **2)** Determine if BrSp supplementation during pregnancy and lactation remediates these aberrant alterations.

Methods: Timed pregnant Long- Evans rats will undergo either bilateral uterine artery ligation on gestational day (GD) 20 of a 23-day gestation to mimic PI, or sham surgery as control. Dietary BrSp supplementation will begin on GD15 and end when the pups are 21 days old. Male and female pups from each litter will be grown to 35 days of age, euthanized, and undergo tissue collection. Brain tissue from both male and female pups per dam will be processed using Golgi-cox staining protocol. Neurons will be traced using a camera lucida and analyzed for dendritic length and complexity using Sholl analysis and branch order, respectively. Three regions will undergo tracing: medial prefrontal cortex (MPFctx), primary motor cortex, and CA1 region of the hippocampus.

Results: Both male and female IUGR pups, with or without BrSp supplementation are significantly smaller at birth, P7 and P35, compared to controls. Data has been completed for experiment 1 in the MPFctx. No significant differences were found in neuronal morphology measurements between IUGR and Sham pups, including, total dendritic length, dendritic intersections, total number of branch points, and branch order.

Conclusions: While our results are preliminary, early findings suggest that behavioural changes seen in IUGR offspring from BUAL dams may not be due to changes in neuronal morphology in the MPFctx. Ongoing work will further delineate the morphology of our model and treatment. In particular, abnormalities in serotonergic or dopaminergic receptor function may be one of the underlying causes.

Funded By: Start-up or Retention Funding

women & children's health research institute

Abstract #: 80
Presenter: Risha Dutt
Supervisor: Cary Brown
Title: Providing the Best Sleep Bedroom Environment for Children with Cerebral Palsy
Authors: Risha Dutt, Cary Brown, Mary Roberts
Affiliations: University of Alberta
Research Activity: Sleep problems in Children
Investigation Type: Quantitative Research

Introduction: Sleep is an active process, essential for physical, emotional and cognitive development of children. Between 23-46% of children with cerebral palsy (CP) have sleep problems. Often sleep problems go undiagnosed and undertreated in spite of the serious impact of sleep deficiency on children's health and development. Interventions, if they are offered, are most often pharmacological. However medication side effects are a significant concern and the evidence- base is lacking. There is a need for effective non-pharmacological intervention to address sleep problems.

Objectives: 1) To determine if providing parents with sleep education and problem solving strategies, in the form of a manual, increases parental knowledge. 2) To determine if increases in knowledge then translation to parents taking actions that decrease sleep negative features in the bedroom.

Methods: This pilot study used a single-case series design. Recruitment of child/parent participants was through community partners. Baseline and 6 week follow-up data collection included the Parental Sleep Environment Knowledge Questionnaire (PSEKQ), Parental Interactive Bedtime Behavior Scale, Child Sleep Habit Questionnaire, Parent Knowledge of Healthy Sleep and objective sleep actigraphy. Parents received the Children's Best Bedroom for Sleep (CBBES) manual (including basic sleep science information, a self-assessment tool, and environmental modification recommendation) as the intervention post-baseline.
Descriptive statistics were used for analysis.

Results: There were 6 parent/child participants. As expected, minimal change was demonstrated in behavioural measures. Parent Sleep environment Knowledge Questionnaire (PSEKQ) improved slightly (66.66% at baseline to 78.33% at follow-up). Also, the bedroom environment assessment checklist provided in the CBBES manual post-intervention results demonstrated improved parent ability to assess their child's bedroom and act to correct problems.

Conclusion: Results support that providing parents with a sleep environment psycho-education manual to build knowledge and skills for addressing environmental components of their child's sleep problems. This research is innovative and will benefit not only children with cerebral palsy and their parents but may also apply to children with other health conditions.

Funded By: CCDS

women & children's health research institute

Abstract #: 81
Presenter: Elma Raissi
Supervisor: Lawrence Richer
Title: Pediatric Emergency Department Investigations for Seizures and the Diagnostic Yield
Authors: Sadaf Raissi, Meghan Linsdell , Lawrence Richer
Affiliations: University of Alberta
Research Activity: Child and Youth Development: Seizures
Investigation Type: Quantitative Research

Introduction: Seizure is a common presenting complaint to the pediatric emergency department (ED). Seizures may occur due to an underlying condition such as a brain lesion and therefore require appropriate investigations when clinically indicated. In an emergency setting, a standardized work up of a seizure prevents errors, saves time, and aids in providing care. This study aimed to identify the prevalence of investigations ordered for a seizure and the diagnostic yield of these investigations.

Methods: This study was a retrospective chart review of 93 children aged less than 18 years of age presenting to the ED between February 1, 2014 to January 31, 2015. The cohort included patients presenting with afebrile seizures with no previous history of seizures, and seizures with a previous history of seizure. The exclusion criteria included head trauma within the last 7 days prior to presenting to the ED. The investigations of interest included computed tomography (CT), magentic resonance imaging (MRI), electroencephalogram (EEG), and lumbar puncture (LP). Any abnormalities from these investigations were deemed medically important if it provided a reason for the presenting seizure.

Results: Of the 93 children presenting to the ED with any case of seizure, there were a total of 31 CT scans, 7 MRI scans, 17 EEGs, and 2 LP procedures completed. Nine of fifty-seven (16%) investigations performed had abnormal results that were deemed relevant to the presenting seizure. In patients presenting with afebrile seizures with no previous history of seizures, n = 56, a total of 34 investigations were performed (CT = 16, MRI = 4, EEG = 13, LP = 1). Eight (24%) results from these investigations were medically relevant to the presentation of the seizure (CT = 5, MRI = 2, EEG = 1). In patients presenting with seizures with a previous history of seizures, n = 37, a total of 23 investigations were performed (CT = 15, MRI = 2, EEG = 5, LP = 1). One (4%) result from these investigations was medically relevant to the presentation of the seizure (EEG = 1).

Conclusion: Our results suggests that investigations in the ED are ordered depending on the clinical scenario at hand. Approximately 33% (31/93) of patients received a CT scan. Less than 20% of patients received an MRI (8%), EEG (18%), or a LP (2%). Diagnostic yield of all the investigations ordered was 16%. This study is a first step in identifying clinical predictors of abnormal investigations in patients presenting with a seizure.

Funded By: WCHRI Clinical Research Seed Grant

women & children's health research institute

Abstract #: 82
Presenter: Parmveer Singh
Supervisor: Heather McDermid
Title: Functional studies of Dnmbp sequence variants found in a cohort of patients with cranial neural tube defects.
Authors: Parmveer Singh, Renee Leduc, Deidre Krupp, Natalie Mola, Erica Davis, Nicholas Katsanis, Simon Gregory, Allison Ashley-Koch, Heather McDermid
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Mixed Methods

Introduction

Neural tube defects (NTDs) are a group of common birth disorders affecting about 1 out of 1000 established pregnancies. NTDs occurs during the formation of the neural system. From a flat neural plate, neurulation creates the neural tube that becomes the brain and spinal cord. The neural plate bends and folds while the ends of the plate meet and fuse to produce the neural tube. If fusion is disrupted, NTDs arise. An open neural tube exposes the neural tissue to the amniotic fluid, leading to neurodegeneration. Both genetic and environmental factors contribute to the formation of NTDs. Our research focuses on the *Cecr2* gene, which encodes a protein involved in chromatin remodelling. Mutation to *Cecr2* leads to a lethal NTD (exencephaly) in mice in a strain dependent manner.
Specifically, 54% of BALB/c mice develop exencephaly, but FVB/N mice do not develop the defect. This suggests the presence of modifier genes effecting the susceptibility. Previously, a modifier region was found on chromosome 19 through a whole genome linkage analysis. Further genetic analyses in mice and screening for variant in human anencephaly patients led to a list of candidate modifier genes, with the most likely modifier being *Dnmbp*. *Dnmbp* regulates actin cytoskeleton and vesicle movement, functions important for proper neural tube formation. I hypothesize that *Dnmbp* is a Cecr2 modifier gene that plays a role in human susceptibility to NTDs.

Methods

Eight human variants of *Dnmbp* were found in probands with an NTD and one mouse variant. *Dnmbp* variants are being singly transfected into cell lines to test whether the variant is deleterious to protein function. Protein localization is being studied in Caco-2 cells using immunofluorescence. I am determining if variants are able to interact with protein partners using co-immunoprecipitation. Lastly, *Dnmbp* is a major activator of Cdc42; thus I will determine if variants are still able to activate this protein.

Results

Thus far, variants of *Dnmbp* have been produced and expressed in cell lines. Irregularities of localization have been observed in one of the variants. Interaction between transfected wildtype *Dnmbp* and two known partners, MENA and VASP, has been confirmed.

Conclusions

While this study is still in progress, abnormalities with one of the variants has already being seen. By characterizing the function, localization, and interactions of Dnmbp variants, we will shed light on a possible NTD susceptibility gene. This study will also further elucidate the complexity of neural system development.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 83
Presenter: Juan Hernandez
Supervisor: Rhonda Rosychuk
Title: Are there regions in Alberta with excess numbers of youth who frequently use the emergency department for mental health reasons?
Authors: Juan F. Hernandez, Dr. Amanda S. Newton, Dr. Rhonda J. Rosychuk
Affiliations: University of Alberta
Research Activity: Child and Youth Mental Health
Investigation Type: Quantitative Research

Introduction: Geographical clustering in the context of health care utilization has not been well-studied. We searched for regions in the province that have a higher number of frequent emergency department (ED) mental health care users than expected to identify potential clusters.

Methods: Using administrative data during 2002-2011, ED presentations for psychiatric disorders and deliberate self-harm for youth aged 10-17 were extracted. Frequent users were defined as youth with ≥2 visits within 12 months. Age-sex directly standardized rates (DSRs) per 100,000 were calculated along with 95% confidence intervals (CIs). Analyses included the spatial scan cluster detection test and logistic regression to assess factors associated with detected clusters.

Results: There were 26,220 patients that had 38,920 ED mental health visits during the study period. 5,019 (19%) patients were classified as frequent users, and accounted for 15,709 (40%) visits. There was a positive trend in the DSR which increased from 144.9 (95% C.I.=132.9, 157.7) in 2004 to 169.7 (95% C.I.=156.8, 183.3) in 2011. Five potential clusters were identified: northern Alberta (Relative Risk [RR]=1.5), Wetaskiwin-Hobbema region (RR = 2.2), downtown Calgary (RR=2.2), and downtown (RR=2.1) and university area (RR=1.6) in Edmonton. Regions identified as clusters were more likely to have First Nations (Odds Ratio [OR]=5.1, 95% C.I.=4.3, 6.1), human services clients (OR = 1.6, 95% C.I.=1.24, 2.06), and government sponsored (OR=1.73, 95% C.I.=1.46, 2.05) individuals than areas that were not part of clusters.

Conclusion: The potential clusters identified may be areas in Alberta where programs can address unmet mental health needs of children and reduce frequent use of emergency services.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 84
Presenter: Ashley Radomski
Supervisor: Amanda (Mandi) Newton
Title: Pilot randomized controlled trial of Internet-based CBT for adolescent anxiety
Authors: Ashley Radomski, Lori Wozney, Patrick McGrath, Alexa Bagnell, Eleanor Fitzpatrick, Sarah Curtis, Mona Jabbour, David Johnson, Rhonda Rosychuk, Michael Young
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Mental Health
Investigation Type: Quantitative Research

Introduction: Anxiety disorders are the most common mental health problem in adolescence, yet are under-recognized and under-treated. Cognitive behavioural therapy (CBT) is a first-line treatment for anxiety, but there are individual, economic, geographical barriers that limit treatment delivery. Online delivery of CBT is emerging as an acceptable alternative among adolescents for increasing access or timeliness of treatment; however, recent reviews suggest further study is needed to establish the treatment effects of Internet-based CBT in children and adolescents and determine economic impacts.

Methods: 'Breathe' is an Internet-based CBT program consisting of 8 interactive and educational modules with personalized homework and telephone/e-mail support, designed to reduce anxiety in youth. We are conducting a 30-month, national, 2-arm parallel-group, pilot randomized controlled trial (RCT) (NCT02059226). Outcomes will inform the planning of a full-scale RCT aimed to test the effectiveness of Internet-based with a population of adolescents with mild-to-moderate anxiety. Across Canada, adolescents aged 13-17 years with an anxiety-based concern can discuss interest and eligibility at a participating emergency department, primary care setting, school or community-based clinic, or can self-refer. Enrolled adolescents are randomly allocated to 8 weeks of Breathe or a control group with access to a webpage listing anxiety resources. Data on recruitment and retention, self-assessed anxiety, intervention use and acceptability, participants' use of co-interventions, and healthcare resource use/costs are being collected electronically at baseline, post-intervention, and 3- month follow-up.

Results: We aim to enrol 80 adolescents (40 assigned to each intervention arm) and expect to retain 40 adolescents (20 per arm) at 8 weeks (post-intervention). To date, 44 adolescents have been screened for eligibility and 19 have been enrolled in the trial. We will present data on the trial's recruitment rate and interim results for participant characteristics.

Conclusions: This pilot RCT is an essential step to designing a robust RCT for evaluating the effectiveness of Internet-based CBT for adolescents with mild-to- moderate anxiety problems.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 85
Presenter: Lauren Albrecht
Supervisor: Shannon Scott
Title: Understanding caregivers' experiences and information needs of pediatric acute gastroenteritis to inform knowledge translation tools
Authors: Lauren Albrecht, Lisa Hartling, Shannon Scott
Affiliations: University of Alberta
Research Activity: child health services research
Investigation Type: Qualitative Research

Background: It is well established that conventional modes of communicating complex health information to caregivers of ill children are substandard due to overuse of complex medical jargon, as well as differences in literacy and health literacy skills. Ensuring that families fully understand essential health information about caring for their ill child is critical to the efficient use of health services and improving health outcomes. Recently novel approaches have been developed to engage with parents and families to translate complex health information, including the use of stories, arts and digital media.

Purpose: To understand caregivers' information needs and preferences related to pediatric acute gastroenteritis to inform the development of two digital knowledge translation tools – a whiteboard animation video and an eBook.

Methods: Caregivers' of children with acute gastroenteritis were recruited in a pediatric emergency department waiting room. Qualitative interviews were conducted to elicit information needs and preferences about pediatric acute gastroenteritis and the decision to come to the emergency department. Thematic analysis was performed using a hybrid inductive/deductive approach.

Results: Fifteen caregivers from diverse backgrounds participated in this study. Thematic analysis revealed five major themes, including: 1) caregiver management strategies; 2) reason for going to the emergency department; 3) treatment and management of acute gastroenteritis in the emergency department; 4) caregiver information needs; and, 5) additional factors influencing caregivers' experiences and decision making. Each of these broad themes contained a number of sub-themes, highlighting diversity within these categories.

Significance: Results will inform the development of two arts-based, digital knowledge translation tools to implement, high quality evidence on pediatric acute gastroenteritis treatment and management. Understanding and incorporating caregivers' perspectives into these tools ensure that critical child health information is communicated in an engaging and effective manner to the people who need it, which may decrease health utilization and improve child health outcomes.

Funded By: CIHR

women & children's health research institute

Abstract #: 86
Presenter: Jillian Avis
Supervisor: Geoff Ball
Title: The Apple of My Eye: Are Parents Accurate Estimators of their Child's Weight Status?
Authors: Jillian Avis, Andrew Cave, Andrea Haqq, Nicholas Holt, Patricia Martz, Raj Padwal, Arnaldo Perez, T. Cameron Wild, Geoff Ball
Affiliations: University of Alberta
Research Activity: Pediatric Obesity
Investigation Type: Quantitative Research

Introduction. Parents' awareness of children's weight status may motivate them to prevent unhealthy weight gain. Our objectives were to *(i)* determine the degree to which parents were able to accurately estimate their child's weight status and *(ii)* identify sociodemographic characteristics of parents based on their estimation accuracy.

Methods. This study reports baseline characteristics of parents and children as part of a randomized controlled trial (RCT) testing a screening, brief intervention, and referral to treatment (SBIRT) program designed to prevent childhood obesity among parents of 5 – 17 year olds recruited from a primary care setting.

Measured height (cm) and weight (kg) data were used to calculate children's body mass index (BMI; kg/m^2), which was subsequently converted to BMI percentiles and weight status categories (*underweight*, *healthy weight*, *overweight*, *obese*). Parents' sociodemographics and perceptions of their child's weight status (*very underweight, a little underweight, just right*, *a little overweight, very overweight*) were collected. Parents were classified as *accurate* or *inaccurate estimators* based on the concordance between their perception of children's weight status and children's measured weight status.

Results. Parents (n=169) of children (mean age: 9.8±3.3 years; mostly *healthy weight* [n=116; 68.6%]) were primarily Caucasian (n=123; 72.8%) and biological mothers (n=144; 85.2%). Almost one-third (27.2%; n=46) of parents misperceived their child's weight status. While most parents underestimated (n=39; 84.8%), some overestimated (n=7; 15.2%) their child's weight status. Most parents (n=33/45; 73.3%) of children with overweight or obesity inaccurately estimated their weight status, a phenomenon that was less common among parents (n=8/116; 6.9%) of children with a healthy weight (c^2 =75.4; p<0.001). Compared to their inaccurate peers, accurate estimators had children with lower BMI percentiles (54.6±25.5 *vs.* 77.0±30.9; p<0.001) and were more likely to be married (c^2 =9.6; p=0.002), Caucasian (c^2 =4.5; p=0.03), and have a post-secondary degree (c^2 =6.3; p=0.01).

Conclusions. Approximately one-quarter of parents inaccurately estimated their child's weight status. Estimation accuracy was associated with children's weight status and parents' ethnicity, marital status, and level of education. Further research, including results generated from our ongoing RCT, is warranted to examine the relationship between estimation accuracy of children's weight status and intended and actual access to health services and educational resources designed to promote healthy lifestyle habits and the prevention of childhood obesity.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 87
Presenter: Sarah Bridgman
Supervisor: Anita Kozyrskyj
Title: Gut microbiota metabolites: biomarkers for early childhood overweight?
Authors: Sarah Bridgman, Petya Koleva, Rupasri Mandal, Meghan Azad, Catherine Field, Andrea Haqq, Allan Becker, Stuart Turvey, Piush Mandhane, Padmaja Subbarao
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Quantitative Research

Introduction: The combined genomes of the gut microbiota contain more than 5 million genes and have a metabolic capacity equivalent to the liver. The gut metabolome is a function of gut microbiota composition and host diet. Differences in fecal short chain fatty acids (SCFA), derived from the microbial fermentation of dietary substrates, have been observed between lean and obese children. Our study is the first to investigate if differences in fecal SCFA composition at 3-4 months of age precede the development of overweight in early childhood.

Methods: Metabolic profiling (using nuclear magnetic resonance (NMR)) of fecal samples taken at 3-4 months from subset of 108 infants enrolled in the Canadian Healthy Infant Longitudinal Study (CHILD) general population cohort was conducted. Infant and maternal characteristics, including breastfeeding status at 3 months of age (none, partial breastfeeding, exclusive breastfeeding), were collected using standardized questionnaires. Anthropometric measurements taken at 3 years of age were used to classify children as normal weight ($<97^{th}$ centile) or overweight/obese ($\geq 97^{th}$ centile) according to BMI-for-age z-scores. Correlations between total SCFA concentrations at 3-4 months of age and BMI z scores at 3 years were conducted using Spearman's rank test. Differences in concentrations of total SCFA (acetate, butyrate, propionate, isobutyrate, valerate, isovalerate) in fecal samples according to weight status at 3 years were tested using non-parametric Mann Whitney test.

Results: 108 (91.5%) of infants were classified as normal weight and 10 (8.5%) as overweight or obese at 3 years of age. Median total fecal SCFA was 19.71mmol/L(IQR 12.98-28.54) in all infants. There was a weak positive correlation between total SCFA concentration at 3-4 months of age and BMIz score at age 3 years (Spearman's rho 0.24, p=0.01). No correlation between SCFA and BMIz score was seen following stratification by breastfeeding status. No difference in median concentration of total SCFA was observed between infants classified as normal weight or overweight/obese at 3 years of age (20.25 and 17.85 mmol/L respectively, Mann-Whitney U, p=0.40).

Conclusion: Our preliminary analysis did not find an association between total fecal SCFA in early life and childhood overweight at 3 years independent of breastfeeding. However, further analysis of individual SCFA and other metabolites is required and may reveal important fecal biomarkers associated with later onset of disease.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 88
Presenter: Samaneh Khanpour Ardestani
Supervisor: Sunita Vohra
Title: Parents and clinicians' voice about probiotic therapy in prevention of pediatric antibiotic-associated diarrhea: Rationale and design
Authors: Samaneh Khanpour Ardestani, Joan Robinson, Levinus Dieleman, Hien Huynh, Hsing Jou, Sunita Vohra
Affiliations: University of Alberta
Research Activity: Research methodology
Investigation Type: Quantitative Research

BACKGROUND:

Antibiotic-associated diarrhea (AAD) occurs as a complication of antibiotic administration. According to two recent systematic reviews, probiotic therapy may be effective to prevent pediatric AAD. However, due to limitations of previous trials, further studies are needed. Some concerns about the primary outcome measure used to date include: (i) lack of justification of minimal important difference (MID); (ii) lack of patient input in developing an MID; and (iii) use of instruments designed to measure the severity of gastroenteritis, rather than AAD.

OBJECTIVES:

1. To establish MID perceived by parents/guardians and clinicians before they would advocate probiotic therapy to prevent pediatric AAD.
2. To obtain parents/guardians and clinicians' opinions about the most important effects of probiotics in pediatric AAD.
3. To design and validate a standardized instrument for assessment of AAD incidence and severity.

METHODS:

In the first phase, a cross-sectional study will be conducted to elicit the opinions of clinicians and parents/guardians of children presenting to the emergency department of Stollery Children's Hospital, Edmonton. Through a paper-based validated questionnaire, using a trade-off tool describing potential harms and benefits of probiotic therapy in AAD, participants will be asked how much benefit they would require from probiotics before using them routinely in children on antibiotics. Additionally, they will be asked about the outcomes that are most important to them in assessing the benefits of probiotic therapy in AAD.

In the second phase, an instrument will be designed based on i) the outcomes identified by parents and clinicians as being most important, ii) relevant constructs of a newly developed core outcome set of pediatric acute diarrhea and iii) a previously validated instrument of pediatric diarrhea. A prospective longitudinal study will be performed to validate the instrument. Children 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 admission and will be followed up daily for two weeks after cessation of antibiotic therapy in order to detect diarrhea incidence and severity. Internal consistency, reliability, content and construct validity and responsiveness will be assessed.

CONCLUSIONS:

Information from the surveys will be applied to calculate the sample size of a future pediatric AAD trial. It also reflects clinicians and parents/guardians' voice regarding important outcomes to measure in pediatric AAD. By designing and validating a standardized instrument, we will be able to accurately quantify pediatric AAD in such a trial.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 89
Presenter: Erin Lewis
Supervisor: Catherine Field
Title: Choline concentration and composition in breast milk is determined by maternal diet
Authors: Erin Lewis, Caroline Richard, Susan Goruk, Yuan-Yuan Zhao, René Jacobs, Jonathan Curtis, Catherine Field
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Quantitative Research

Introduction

Maternal requirements for dietary choline increase during lactation to provide choline in breast milk to meet the high needs of the developing infant. We have previously reported that women consume different amounts and forms of choline, the most abundant forms being phosphatidylcholine and free choline.
Evidence from rodents suggests that lactating dams are more dependent on dietary choline compared to non-lactating dams and that the forms of choline have different bioavailabilites. However, the effect of different amounts and forms of choline in the maternal diet on breast milk choline composition is not well understood. The objective of this study was to examine the choline composition in breast milk from lactating Sprague Dawley rat dams fed varying amounts and forms of dietary choline.

Methods

From birth to weaning (21 days), dams were fed nutritionally complete, isocaloric diets, differing only in amount or form of choline provided; Devoid (D) (0 g choline/kg diet), Choline (C) (1 g choline from free choline/kg), Phosphatidylcholine (PC) (1 g choline from PC/kg), Mixed Choline (M), modelled after the dietary pattern in our maternal-infant cohort (1 g choline from 50% PC, 25% free choline, 25% glycerophosphocholine/kg). Stomach contents (representing breast milk) from 3-week old pups was collected and analyzed for choline-containing metabolites and total choline by LC-MS/MS.

Results

D dams had lower breast milk total choline content (78 ± 33 ug/g) compared to dams fed C (120 ± 12 ug/g), PC (146 ± 20 ug/g) and M (179 ± 13 ug/g) diets containing sufficient choline (all $P<0.05$). C dams had a higher proportion of total choline as free choline (31% ± 2% of total choline) compared to PC dams. Conversely, PC dams had a higher proportion of total choline as lysophosphatidylcholine (10% ± 2%) and glycerophosphocholine (39% ± 3%) compared to C dams ($P<0.05$). Composition of milk from M-fed dams was reflective of dietary forms of choline, with a higher proportion of total choline as PC (25% ± 5% of total choline) and a lower proportion of total choline as free choline (17% ± 4%) and phosphocholine (5% ± 1%) ($P<0.05$).

Conclusions

In summary, we demonstrate that choline concentrations in breast milk are influenced by both amount and form of choline in the maternal diet. This is of importance as our prior work demonstrated that women are consuming below daily recommendations for lactation and the amount and form of choline influences maternal immune function and immune development in their offspring.

Funded By: Dairy Farmers of Canada, NSERC, Alberta Livestock and Milk Association

women & children's health research institute

Abstract #: 90
Presenter: Krista MacDonald
Supervisor: Diana Mager
Title: Influence of adiposity and insulin resistance/hyperinsulinemia on vitamin D status in nonalcoholic fatty liver disease (NAFLD): A systematic review
Authors: Krista MacDonald , Andrea M. Haqq, Jason Yap, Diana R. Mager
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Qualitative Research

Introduction: Nonalcoholic fatty liver disease (NAFLD) has been reported in 20-30% of obese individuals. NAFLD is a chronic liver disease that encompasses a spectrum of liver disease ranging from simple steatosis to steatosis with inflammation or fibrosis (non-alcoholic steatohepatitis) and cirrhosis. NAFLD may represent the liver expression of the metabolic syndrome. Studies have shown that individuals with NAFLD have lower serum 25-hydroxyvitaminD (25(OH)D) levels, but the mechanism for this is unknown. This systematic review examined the evidence relating adiposity, insulin resistance (IR) and hyperinsulinemia and vitamin D (vitD) status in individuals with NAFLD.

Methods: Medline, Embase, Pubmed and Web of Science databases were searched using key words for NAFLD and vitD in combination with body composition or IR/hyperinsulinemia. Studies were primary research articles (English), on human subjects (all ages) with NAFLD, in which the relationship between 25(OH)D and anthropometric/body composition measurements were evaluated. Anthropometric measurements included circumferences or skinfolds and BMI. Body composition measurements included bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and/or computed tomography (CT). Relationships between 25(OH)D and IR/hyperinsulinemia were also evaluated. Articles were excluded if the primary focus was on participants with chronic diseases (type 2 diabetes mellitus or cardiovascular disease).

Results: Thirteen studies (1 intervention/12 observational) met the inclusion criteria (506 records identified, 444 excluded during title/abstract review and 49 during full-text assessment). Studies varied in population (age/gender) and methods used to assess vitD status, NAFLD and body composition and confounding factors known to influence primary outcomes. The calculable effect sizes for the significant differences in: 25(OH)D concentrations were small (17%), medium (17%) and large (67%), IR/hyperinsulinemia measurements were medium (40%) and large (60%) and body composition measurements were small (20%), medium (40%) and large (40%). Evidence from observational studies suggests that lower 25(OH)D levels are related to visceral fat area and HOMA-IR, however these results are inconsistent. Most studies had fair to good quality assessment scores. Overall, the strength of evidence is weak and of moderate quality (level
B) (Chalasani, 2012).

Conclusions: Future studies are needed to assess the mechanisms behind why vitD status is influenced by IR and adiposity and as well interventions to see if vitD supplementation improves IR/hyperinsulinemia and body composition. This is important for more serious liver disease, as currently there are few effective therapies.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 91
Presenter: MON TUN
Supervisor: ANITA KOZYRSKYJ
Title: Impact of infants' exposure to hospital microbial environment on gut microbiota composition at 3 months
Authors: MON TUN, PETYA KOLEVA, JAMES SCOTT, DAVID GUTTMAN, MALCOM SEARS, PIUSHKUMAR MANDHANE, STUART TURVEY ALLAN BECKER, FELIX RATJEN, ANITA KOZYRSKYJ
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Background:

The early establishment of gut microbiota in a newborn infant is thought to be important for the development of the immune system. Although extensive research has been conducted to investigate the effects of delivery mode and infant feeding on gut mircobiota, not much is known about the influence of hospital microbial environment on infant microbiota composition and diversity. The aim of this study is to investigate the impact of infant early life hospitalization on the gut microbiota.

Methods:

A subset of 422 samples from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort from Edmonton and Winnipeg sites were included in the study. Infant hospitalization history was obtained from standardized questionnaire at 3 months post partum. Faecal samples at 3 and 4 months were characterized by Illumina 16S rRNA sequencing. Microbiota diversity and richness were determined using Shannon and Chao1 estimators, respectively. The gut microbiota profile of infants with hospitalization history (n=341, 80.8%) was compared to the profile of infants without hospital admission history (n= 81, 19.2%). Comparisons were performed with Mann-Whitney U-test.

Results:

At the phylum level, Bacteriodietes (p=0.001) was less abundant, whereas Proteobacteria (p=0.037) was more abundant in infants with a hospitalization history in the first 3 months. Furthermore, the same trend was observed at the family level for their respective families, *Bacteroidaceae* (p=0.001) and *Enterobacteriaceae* (p=0.026). In addition, *Enterococcaceae* (p= 0.010) and *Ruminococcaceae* (p=0.033) were more abundant in hospitalized infants. The same trend of differences was also detected in a comparison restricted to vaginally- delivered, exclusively breastfed, and not treated with antibiotic infants.

Additionally, reduced diversity at order level (p=0.07) and more richness of *Bacterioidetes* (p=0.001) was detected in all infants who were admitted to hospital within first 3 months of life.

Conclusion:

This study highlights the association between hospitalization in first 3 months and early infant gut microbiota composition with decreasing overall diversity and increasing richness of certain species.

Funded By:

Abstract #: 92
Presenter: Mandy Archibald
Supervisor: Shannon Scott
Title: Arts for Asthma? A Critical Review of the Arts in Childhood Asthma Education, Research, and Practice
Authors: Mandy Archibald
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Sleep and Breathing Disorders
Investigation Type:

Introduction: In various health care contexts, the arts are gaining traction as powerful methods for communicating health information, illuminating illness experiences, and as viable therapeutic approaches. Arts-based methods (e.g., visual arts, storytelling) may facilitate engagement with health information; appeal to multiple literacy levels, populations, and cultural groups; and reveal experiences of health and illness in ways that non-emotive communications, such as traditional text-based correspondence, cannot. Arts-based approaches may hold particular promise for childhood asthma, given asthma's global prevalence, the persistent challenges in improving childhood asthma outcomes, and the complexity and associated challenges of asthma self-management. However, no research has examined how the arts have been used for childhood asthma. Research is needed to locate potentially usable and effective approaches that integrate the arts in asthma care and to identify promising areas for future inquiry.

Methods: A critical review is underway to identify how the arts have been used in the context of childhood asthma. CINAHL, MEDLINE, were searched using no date limiters and using variations of arts, pediatric, and asthma key words. Ancestry searching will be used to identify other relevant articles not captured in the initial search. Two types of documents will be included in the review: (I) arts-based childhood asthma resources and (II) articles discussing the use of the arts in childhood asthma.

Results: 452 potentially relevant articles were located through database searching *CINAHL n=98; MEDLINE n=354).* 64 duplicate articles were removed and 13 articles met inclusion criteria.Google is currently being searched to locate web-based asthma tools. Analysis is ongoing; however, preliminary findings show that the arts are most often used in data collection for school-aged children, and focus on the illness experience. Four asthma educational tools for school-age children were also identified and utilized various visual and story-based techniques. Additional analysis will examine (a) the intended audience for the arts-based methods, (b) the rationale for using an arts-based approach; (c) the artistic form used; and (d) evaluation methods and results. In addition, the following data will be extracted for arts-based educational materials: (a) the evidence-base, (b) format (e.g., booklet, audiovisual); (c) development location; (d) developer credentials; and (e) dissemination and implementation strategies.

Conclusions: As arts-based methods become increasingly integrated into health care practice and research, there is a need to take-stock of available resources; to identify strengths, limitations of existing approaches; and detect areas where additional resources are needed to support childhood asthma care and self- management.

Funded By: Partnership resources

Abstract #: 93
Presenter: Annie (Sudi) Duan
Supervisor: Silvia Pagliardini
Title: Probing respiratory network connectivity with viral constructs and optogenetics
Authors: Annie (Sudi) Duan, Silvia Pagliardini
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Sleep and Breathing Disorders
Investigation Type:

Introduction:

Breathing in mammals is most fragile during sleep, in particular during rapid eye movement (REM) sleep when breathing is more irregular and it may be interrupted by pauses (apneas), which are associated with drop in oxygenation. A small cluster of neurons in the brainstem, the parafacial respiratory group (pFRG) recruits expiratory abdominal muscles, as shown previously in our laboratory. Further results from our laboratory suggest that recruitment of abdominal muscles occurs during REM sleep and it is associated with improved minute ventilation and more regular breathing.

The goal of this study is to investigate the projections to the pFRG of several brainstem structures that are involved in sleep-wake dynamics, in order to determine their influence on ongoing respiration and on the activity of the pFRG.

Methods:

We used adult male rats injected with a combination of retrograde Cre-recombinase viral tracers and optogenetic Cre-dependent viruses. 3-4 weeks post- injection, animals were perfused and the expression of viruses analyzed with immunohistochemistry.

Results:

We have identified several nuclei of interest (nucleus of solitary tract, ventral respiratory column) in the brainstem that project to the pFRG through retrograde tracer experiments.

Conclusion:

Currently, we are still in the process of investigating these projections and their role in pFRG activation and in respiration.

Funded By: Summer Studentship

Abstract #: 94
Presenter: Alexis Katzell
Supervisor: Gregory Funk
Title: Inspiratory burst termination: Could M-current be the answer?
Authors:
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Sleep and Breathing Disorders
Investigation Type: Quantitative Research

Introduction

"What terminates the inspiratory burst?" remains a major unanswered question in respiratory neurobiology. Mechanoreceptive, inhibitory feedback from the lungs is key during normal quiet breathing but in the absence of this information inspiration still stops. The M-current, so-named for the inward current evoked by muscarine when it blocks these channels, is active at resting membrane potential. It becomes larger with membrane depolarization, and therefore acts to stabilize membrane potential by counteracting depolarization. During rhythmic activity, we reasoned that as the membrane potential of inspiratory neurons depolarizes, the progressive activation of the M-current may help terminate the burst. KCNQ genes encode for the Kv7.2/7.3 channel subunits believed to be principle components of the channel that carries the slow voltage-gated M-current. The role of this channel in inspiratory rhythm has received minimal attention. Blockade facilitates repetitive discharge in sympathetic neurons, sensory nociceptive systems, and hippocampal pyramidal neurons. We tested the hypothesis that blockade of the M-current block would prolong inspiratory burst duration.

Methods

We used rhythmically-active medullary slice preparations (700 µm thick) that generate inspiratory-related activity and measured the frequency (freq), amplitude, burst duration, and interburst interval of the inspiratory rhythm recorded from the XII nerves before and during bath application of XE991 (0.1µM and 1µM; blocker of M-current). Drug effects were measured over a 2 minute period in control, after 30 minute and 60 min of drug exposure and after 2 hours of washout.

Results

The effects of XE991 on inspiratory rhythm increased progressively both with time and concentration. Following 1 hour exposure to 1 µM XE991, inspiratory burst duration increased by 259 ± 44% (n=5), burst frequency decreased by 48 ± 6%, and interburst interval increased by 56 ± 26%. Inspiratory burst duration returned toward control after a 2 hour washout period.

Conclusions

The dramatic increase in burst duration following block of the M-current suggests that it plays an important role in inspiratory burst

termination. Funded By: Summer Studentship

women & children's health research institute

Abstract #: 95
Presenter: Jasmeen Saini
Supervisor: Silvia Pagliardini
Title: Respiratory Muscle Recruitment in Neonatal and Juvenile Rats Across Sleep States
Authors: Jasmeen Saini, Colin Andrews, SIlvia Pagliardini
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Sleep and Breathing Disorders
Investigation Type: Mixed Methods

Introduction (purpose)

Breathing in humans and rodents is fragile during sleep, specifically during rapid eye movement (REM). Premature and full-term infants often present sleep- related breathing disorders (SBD) due to the immaturity of the respiratory system and the neuronal networks that control rhythmic respiratory muscle recruitment. Little is known about expiratory activity in young rats, in particular across sleep states, and its relative contribution to ventilation. We hypothesize that in juvenile rats expiratory muscle activity is recruited during sleep when respiration is more irregular, associated with an increased stability of respiratory rhythms.

Methods

Neonatal and juvenile rats (post-natal day, P3,7,14) were implanted with EMG electrodes in the neck, intercostal and abdominal muscles to measure: sleep states, inspiratory activity and expiratory activity respectively. Rats were recorded inside a whole body plethysmograph to measure respiratory flow and video monitored to confirm sleep state changes. In the P14 groups, EEG activity was also measured by means of cortical electrodes. The EMG/EEG signals and airflow traces from the plethysmograph were acquired with a Powerlab acquisition system. Data was analyzed with LabChart software and statistical data analysis was performed in Excel and Origin softwares.

Results

Results indicate that recruitment of expiratory modulated abdominal activity during REM see improved respiratory stability, increased tidal volume and minute ventilation.

Conclusion

Research in our lab suggests that that expiratory activity may be critical in the neonatal period, when respiratory activity is more likely to fail, to prevent breathing irregularities and to strengthen inspiratory activity. The recruitment of abdominal muscles is more frequent in juvenile rats compared to adult and unlike adults is present in both active and quiet sleep.

Funded By: Summer Studentship

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Abstract #: 96
Presenter: Areej Alhhazmi
Supervisor: Gregory Tyrrell
Title: A novel GBS Immunogenic Bacterial Adhesin BibA Variant that Associated with Capsular Polysaccharide Type IV and Invasive GBS Infections in Adults
Authors: Areej Alhhazmi
Affiliations: University of Alberta
Research Activity: Women's Health : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: The Group B streptococcus (GBS) is an important pathogen of neonates. To cause disease, GBS utilize a variety of virulence factors including a capsular polysaccharide and a surface protein, BibA. There are currently 10 capsule polysaccharide serotypes (CPS); Ia, Ib, II-IX. CPS Ia, Ib, III, and V are common whereas the others are less so. There are 4 BibA variants (bibA I, II, III and IV). GBS can also be typed via multi-locus sequence typing (MLST). A major hypervirulent MLST clone currently circulating globally is the clonal complex (CC) – 17. This clone possesses bibA IV and is usually present in CPS III. There have been recent reports of CPS IV that encode CC17 specific bibA IV. From 2008 to 2013, there was an increased in CPS IV GBS disease in Alberta. Our objective was to characterize the CPS IV associated with this increase and determine if these isolates are part of the global CC17 expansion.

Methods: A described bibA IV-specific PCR was performed on CPS IV collected from Alberta (2003-2013). Based on the bibA results, we performed MLST on CPS IV from 2013 (22 isolates) and four other GBS CPS IV isolates from 2003, 2009, 2010 and 2011. Multiple sequence alignment and a phylogentic tree of bibA sequences from the Alberta CPS IV isolates and bibA contained in GenBank was performed using MUSCLE and UPGMA. A bibA variant specific PCR was also designed and performed on all 2013 isolates once the novel bibA variant was identified.

Results: Based on the bibA IV PCR assay, 91/106 (85.9%) of the CPS IV assayed possessed the bibA IV. MLST revealed CPS IV clustered in the CC-1 complex (distantly related to CC-17). The bibA sequences from the 4 CPS IV/CC-1 displayed low identity with bibA I, II, III and IV. Phylogenetic tree of the known bibA variants plus the new bibA sequences from the CPS IV revealed three distinct lineages. Lineage II exclusively consists of the 4 CPS IV strains suggesting that these strains encode a novel bibA variant. Fourteen isolates from Alberta 2013 collection found to possess the new bibA sequence. Further analysis revealed that this variant was found in CPS IV (10/14, 71.4%) and was more frequently associated with soft tissue and adult infections (8/14; 57.1% and 13/14; 93%).

Conclusion: The increased numbers of Alberta GBS CPS IV were found to encode a new bibA variant that is associated with soft tissue infections in adults. Funded By: High ministry of education saudi arabia

women & children's health research institute

Abstract #: 97
Presenter: Zaki Alsahafi
Supervisor: Silvia Pagliardini
Title: Cholinergic modulation of the expiratory rhythm generating center (parafacial respiratory group) in adult urethane anesthetized rats
Authors: Rozlyn Boutin, Zaki Alsahafi, Silvia Pagliardini
Affiliations: University of Alberta
Research Activity: Respiratory
Investigation Type:

Introduction

Active inspiratory and expiratory activities are respiratory phases generated by two separate oscillators in the brainstem, with inspiration driven by a network of neurons located in the preBötzinger Complex (preBötC) and expiration driven by a network of yet unspecified neurons in the para facial respiratory group (pFRG). While continuous activity of preBötC is necessary for maintaining ventilation, the activity of pFRG appears to be dependent on presence of respiratory drive (hypoxia, exercise, release of inhibition, excitatory neuromodulation), acting therefore as a conditional oscillator, silent at rest and recruited in conditions of high respiratory drive.

Recent evidence suggests that expiratory activity in the principal expiratory muscles, the abdominal muscles, is state dependent modulated and occurs in periods of REM sleep

Methods

Adult male Sprague-Dawley rats (280-350g) were used for acute experiments. Rats were anesthetized, vagotomised and EMG electrodes were implanted. Carbachol (CCH, 10mM, 100nl), Scopolamine (SCOP; 10mM, 200nl), physostigmine (PHYSO, 5mM, 200nl) diluted in HEPES buffer pressure injected through a sharp glass electrode into the pFRG.

Results

We demonstrate that local application of carbachol, a cholinergic agonist, into the pFRG activates long lasting rhythmic expiratory activity. This effect was completely abolished by pre-application of the muscarinic antagonist scopolamine and reversed after a 2hr washout period. In addition, local application of the acetylcholinesterase inhibitor physostigmine, gradually increases endogenous acetylcholine locally and potentiate expiratory abdominal activity.

Conclusion

These results demonstrate that cholinergic muscarinic transmission contributes to excitation of pFRG neurons and promotes active recruitment of ABD_{EMG} activity and active expiratory flow.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 98
Presenter: Uday Chauhan
Supervisor: Craig Steinback
Title: Mechanisms of sex differences in breath-holding performance
Authors: Uday Chauhan, Christina Bruce, Rachel Skow, Maria Abrosimova, Jamie Pfoh, Trevor Day, Margie Davenport, Craig Steinback
Affiliations: University of Alberta
Research Activity: Mechanisms of sex differences in breath-holding performance
Investigation Type: Quantitative Research

Introduction

Present world records for breath-holding are 11:35min for males and and 9:02min for females. Breath holding performance is influenced by a variety of factors including chemoreflex drive to breathe (i.e. dependent on arterial O2 and CO2) and lung volume/stretch. The mechanisms regulating differences in breath- holding time between males and females have not been determined. The present study aims to determine the independent influences of lung volume/stretch and chemoreflex drive in mediating potential sex differences in breath hold regulation. We hypothesize that breath hold ability differs between males and females due to differences in both chemoreflex drive (to hypoxic and hypercapnic stimuli) and lung volume/stretch.

Methods

We studied 13 women (age 23.5±3.2 yrs) and 11 men (26.3±4.6 years) during 4 maximal apneic maneuvers designed to isolate the independent influence of lung stretch and chemoreflex drive; 1) end-tidal expiratory (ETE), 2) end-inspiratory (INSP) designed to isolate the influence of lung volume, 3) INSP following hyperventilation to isolate the influence of hypoxic drive (HX), and 4) INSP following hyperoxic breathing to isolate the influence of hypercapnic drive (HC).
Spirometry was conducted on all participants, with men having a larger forced vital capacity (FVC; 5.8±0.9L) and total lung capacity (TLC; 7.3±1.0L) compared to women (4.2±0.5L, $p<0.001$ and 5.3±0.5L, $p<0.001$ respectively).

Results

There was no difference in ETE duration between men and women (33.2±18.2 vs 38.9±18.4s) suggesting that stature and lung size did not influence breath-hold performance. Men and women both had longer INSP durations compared to ETE; however, men had a significantly longer INSP duration (112.4±48.3) compared to women (75.0±32.7s, $p<0.05$). Men also had longer HX (158.1±39.4s) and HC (184.7±61.3s) breath-holds compared to women (113.8±25.6s, $P<0.01$ and 125.7±46.4s, $p<0.05$ respectively). After taking into account the influence of INSP, these differences were no longer apparent, suggesting a primary influence of inspiration. Correspondingly, FVC ($r2=0.189$, $P<0.05$) and TLC ($r2=0.188$, $P<0.05$) were correlated with improvement in breath-hold duration with INSP, but only when both sexes were included in the analysis.

Conclusion

These data suggest that men have a significantly increased capacity for breath-holding compared to women across a range of inspiratory (but not expiratory) maneuvers. This increased capacity is dependent on factors related to lung volume, and perhaps more specifically lung stretch, and not chemoreceptor drive.

Funded By: NSERC, HPF

women & children's health research institute

Abstract #: 99
Presenter: Parvaneh Badri
Supervisor: Maryam Sharifzadeh-Amin
Title: Life Course Factors Associated With Dental Caries: A Systematic Review
Authors: Parvaneh Badri, Lucas Guimaraes Abreu, Maryam Elyasi, Saul Martins De Paiva, Carlos Flores-Mir, Maryam Amin
Affiliations: University of Alberta
Research Activity: Child Oral Health
Investigation Type:

Introduction: The life course approach places a great emphasis on a large range of experiences at difference stages of life, which ultimately contribute to the development of chronic diseases later on.

Objectives: To conduct a systematic review of studies that used the life course approach to evaluating the association between factors experienced in early life and throughout the lifetime and the development of dental caries in children and adolescents.

Methods: A systematic search of electronic databases was carried out using Medline (Ovid SP), PubMed, Embase (Ovid SP), Scopus (Elsevier), and Web of Science (Thompson Reuters). The hand search of the reference lists of the included articles and gray literature search by using Google Scholar and Google search engine were also performed. We selected only quantitative studies that adopted the life course approach to examine the factors associated with the development of dental caries in children and adolescents. Titles and abstracts were screened by 2 reviewers. Reports with relevant abstracts received full-text review and were examined for inclusion in the present systematic review. Due to the high degree of heterogeneity, the meta-analysis was not feasible.

Results: A total of 1,571 potentially relevant records were found in the five databases, 373 of which were duplicated. Additionally, one record was identified through the gray literature. Thus, the abstracts of 1,199 studies were read. A total of 1,151 references were excluded based on the abstracts, and 48 were selected for full-text analysis, 37 of which did not fulfill the inclusion criteria. Therefore, of the 48 full reports initially selected, 11 were included.

Conclusions: There was an association between life course factors and the development of dental caries in children and adolescents. The life course approach provides the useful ground for dental research in addressing the structural determinants of socioeconomic, biological, psychosocial, and behavioral aspects and their subsequent relationship to oral health over time. Such information may also be of great value to health planners, since dental caries places a considerable burden on oral health care globally.

Funded By: Trainee Travel Grant

women & children's health research institute

Abstract #: 100
Presenter: Maryam Elyasi
Supervisor: Maryam Amin
Title: Impact of parental sense of coherence on their children's oral health-related behaviors
Authors: Maryam Elyasi, Cheyanne Olsen, Lucas Abreu, Maryam Amin
Affiliations: University of Alberta
Research Activity: Children Oral Health
Investigation Type: Qualitative Research

Introduction:

Promising oral health habits are established in early childhoodand their development is primarily mediated by parental behaviours. While considering psychosocial factors, parents' ability to cope with daily stressors has an important role in identifying and mobilizing resources to control children's oral health practices. The ability to deal with life-stressors has been investigated through the concept of Sense of Coherence (SOC). Our objective was to assess the impact of parents' SOC on their preschooler's dietary and toothbrushing behaviours.

Methods:

A cross-sectional study is ongoing with parents of preschoolers. A convenience sample of 380 parents are recruited from the immunization programs run by different community health centers. Demographics, children's oral habits, and parents' SOC measures are collected. Parents' SOC is measured by the validated SOC questionnaire (13-items) on a Likert scale. The SOC score is the sum of answers, with higher scores indicating stronger SOC. Associations between the independent variable (SOC) and outcome variables (frequency of toothbrushing, intake of sugary snacks) are assessed by two-sample *t* tests and multiple logistic regression analysis.

Results:

Data presented is based on 195 participants with mean age of 34.15 + 4.9 years; 77.6% of them had a post-secondary education and 83.1% had a household monthly income of > $3000. The mean age of children (half boys) was 4.39 ± 0.73 years, 78.3% of them had dental coverage. After adjustment for identified confounders (parent education and family monthly income) the association between child's sugar intake and parent's SOC was attenuated but remained statistically significant (P=0.036). However, the association between child's toothbrushing and parent's SOC was fully attenuated after considering those confounding variables (P=0.090).

Conclusions:

Parent SOC does affect child oral health behaviours (daily intake of sugary foods). This information may have implications for development of oral health promotion and intervention programs designed to improve oral health of young children through strengthening parents' SOC.

Funded By:

women & children's health research institute

Abstract #: 101
Presenter: Basmah Al Jabri
Supervisor: Debra Andrews
Title: Training needs for developmental pediatrics in Saudi Arabia
Authors: Basmah Al Jabri
Affiliations: University of Alberta
Research Activity:
Investigation Type: Quantitative Research

Background:

Developmental pediatrics (DevPeds) is a core branch of general pediatrics. A 1-2 month DevPeds rotation is mandatory in Canada and the United States. Until recently there was no mandated DevPeds rotation in Saudi Arabia; however, in October 2014 this changed.

There are few published articles about DevPeds conditions in Saudi Arabia and none about DevPeds training. We evaluated perceived educational needs of practicing Saudi general pediatricians who completed their training in the past five years and current trainees.

Methodology:

Saudi Arabia trainees who completed pediatric residency training in the last fiveyears (from 2010-2014) or who were still in training were approached for participation through the Saudi Commission of Health Specialties (SCHS). Because many registered Saudi physicians did not give e-mail, both e-mails and text messages with a letter describing study objectives and the survey link were sent out.

Results:

The response rate was 33% (n=174). Consultant pediatricians (who are in clinical practice more than 2 years after obtaining a Board degree as classified by SCHS) represented 33% of the sample, 12% were specialists (who spent 2 years only in clinical practice after obtaining a Board degree), 15% were subspecialty residents, and 17.5 % were still in training.

For the whole group: 51% of their practice consisted of developmental conditions. 39% of them believed that they need much more training in this field. Learning opportunities about developmental conditions during residency were available to 55% of the participants. DevPeds training was classified as "important " or "very important" by 95%, and 48% requested to have 2-month rotation during residency training.

Conclusion:

Practicing pediatricians in Saudi Arabia reported that developmental conditions comprised more than half of their practice, and indicated a need for more DevPeds training in residency. Our study supports a mandatory DevPeds block in pediatric residency training in Saudi Arabia with well-defined training objectives and clear assessment tools of residents' knowledge and skills.

Funded By:

Abstract #: 102
Presenter: Anne Halpin
Supervisor: Simon Urschel
Title: Homografts and HLA: A challenge in pediatric heart transplantation
Authors: Nassiba Alami Laroussi, Anne Halpin, Luis Hildalgo, Patricia Cambell, Lorie West, Jennifer Conway, Simon Urschel
Affiliations: University of Alberta
Research Activity: Maternal Research : Cardiology
Investigation Type: Qualitative Research

Introduction

The Norwood Procedure includes vascular prostheses from human donors tissue (homograft) that can allo-immunize patients thus complicating future transplant. A case study is presented that highlights this issue.

Methods

A 9 year old with a history of hypoplastic left heart syndrome was listed for heart transplant. In 2002 she received untreated homograft as part of this repair;
there is no knowledge of the donor HLA. She developed protein losing enteropathy (PLE) following a 2006 Fontan surgery.

As part of her work-up for transplant, she was screened for HLA antibodies. She was also typed for all HLA loci. A T and B cell flow cytometry crossmatch was performed.

Results

At the time of listing, several strong class I and class II HLA antibodies were identified: Anti-B8, B59, B46, DR15, and DR16

Mismatched donor HLA antigens: A3 A31 B37 B60 Cw6 Cw10 DR10 DQA1*01 DQB1*03:02 DQB1*05 DPB1*02:01P. The virtual crossmatch was negative based on previous antibody results.

The pre-transplant crossmatch was T and B cell negative with historic serum but B cell strong positive with current serum.

STAT antibody identification revealed additional strong donor specific antibodies (DSA) to DQ5 and moderate antibody to DR10 explaining the positive B cell crossmatch. Thymoglobulin, Rituximab and plasmapheresis were initiated.

Day 7 biopsy AMR grade 2 (histology and C4D positive). Bortezomib IV was given on Day 9,13,16, and 20. Eculizumab was given Day 12 and plasmapheresis was held.

Day 21 biopsy AMR 1; Histology positive but decreased in severity and C4d

negative. Strong antibody to DQ5 remains, but the two subsequent biopsies have

no AMR. Conclusions

Homografts are sensitizing event and often the donor HLA type is unknown. Patients with HLA antibodies are at risk for antibody mediated rejection at transplant. Antibody specificities can change over time and be falsely negative in a situation of PLE thus reducing the reliability of the virtual/predicted crossmatch results.

This risk can be reduced by: HLA typing and matching of homografts, reducing allogenicity of homografts (glutaraldehyde treatment), and repeat testing for patients with protein losing enteropathy and low levels of serum immunoglobulins. Pre-transplant desensitization may also be attempted to avoid intense AMR treatment as necessary in this patient.

In this patient and others who have pre-transplant DSA or develop *de novo* DSA, the long-term prognosis is unclear.

Funded By:

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Abstract #: 103
Presenter: Jag Bhogal
Supervisor: Po-Yin Cheung
Title: High Frequency Oscillation with Volume Guarantee has less negative impact on Cardiac Index compared to Conventional Ventilation in Piglets with RDS
Authors: Jag Bhogal, Anne Solevag, Georg Schmolzer, Po-Yin Cheung
Affiliations: University of Alberta
Research Activity: Paediatric medical science
Investigation Type: Quantitative Research

Introduction: High frequency oscillatory ventilation (HFOV) is commonly used as rescue therapy for neonatal respiratory distress syndrome (RDS). "HFOV with volume guarantee" (HVG) is a new modality that may maintain intrathoracic pressure and blood gas homeostasis. We aimed to compare the hemodynamic effects of HVG with the "non-VG" mode (HnoVG) and conventional ventilation (CMV) using a newborn piglet model of RDS. We hypothesized that HVG would have the least negative systemic and regional hemodynamic effects when compared with HnoVG and CMV.

Methods: Piglets (1.4-2.4 kg; 1-3days old) were anesthetized and instrumented. Left ventricular (LV) output, common carotid and renal artery flows were measured using a Millar® catheter and Transonic® flow probes, respectively. LV, carotid and renal artery flow were indexed for body weight as "CI", "CAFI", and "RAFI". Cerebral and renal tissue oxygenation was measured by near-infrared spectroscopy (Invos®). Bronchoalveolar lavage was performed to achieve an alveolar-arterial O2 gradient (AaDO2) of 300-450mmHg to simulate moderate to severe RDS. Piglets were then block-randomized to CMV, HnoVG, or HVG for 4 hours. Sham-operated piglets without RDS were monitored for the same duration under CMV.

Results: RDS was induced in 24 piglets (n=8 per group, n=6 for sham). AaDO2 values and mean airway pressures were comparable among groups ($P>0.05$). There were modest decreases in CI and mean arterial pressure (MAP) with CMV. HVG had a significant decrease in CAFI and MAP in the last 2 hours. RAFI, AaDO2 values, and mean airway pressure were similar among the groups. The oxygen extraction ratio seemed to trend higher with HVG mode.

Conclusions: Newborn piglets with RDS appeared to have some differences in systemic and regional perfusion between ventilation groups. HVG trended towards a lower MAP and CAFI, as well as towards a higher oxygen extraction over time. CI appeared to trend lower over time in the CMV group. Further examination of cardiac function from Millar® catheter data will facilitate detailing more hemodynamic effects.

Funded By:

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Abstract #: 104
Presenter: Luke Eckersley
Supervisor: Lisa Hornberger
Title: Haemodynamics and left ventricular myocardial function in fetal Ebstein's anomaly / tricuspid valve dysplasia.
Authors: Paul Brooks, Nee Khoo, Lisa Hornberger
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction

Fetal Ebstein's anomaly and tricuspid valve dysplasia (EA/TVD) are rare congenital cardiac defects associated with a very high mortality. In more severe disease with insufficient right ventricular output, the cardiac preload must be redistributed to the left heart, as observed in the single left ventricle (SLV). Left ventricular (LV) systolic dysfunction in third trimester fetal EA/TVD is associated with perinatal mortality, and ventricular interactions have been postulated to be an important factor. We have shown the fetal SLV increases sphericity and circumferential deformation, but not longitudinal strain to augment preload and maintain cardiac output, however little data exists on LV mechanics in EA/TVD. In this investigation, we examined LV function in fetuses with EA/TVD compared to SLV and healthy controls.

Methods

This was a retrospective case-control analysis of all fetal diagnoses of EA/TVD in the Fetal and Neonatal Cardiology Program since 2005. Hemodynamic, global functional parameters and myocardial mechanics were analysed using Siemens Syngo 2.0. Groups analysed included EA/TVD with retrograde ductal flow (EA-R), EA/TVD with antegrade ductal flow (EA-A), SLV and controls. Presented p-value Kruskal-Wallis non-parametric test (SPSS V.22).

Results

We identified 29 fetal diagnoses of EA (20) and TVD dysplasia (9), (including 12 EA-A and 17 EA-R), 29 SLV and 43 controls. Perinatal and infant mortality for EA/TVD fetuses was 17/29 (58.6%). Of actively treated EA/TVD cases, ductal flow was antegrade in 9/11 (82%) survivors, but only 3/9 (33%) of those who demised. Hemodynamic assessment was completed in all patients, and myocardial mechanics in 15/29 to date. The LV diameter was larger in the SLV and EA-R group than the EA-A group or controls (mean±SD 12.0±4.9, 12.3±3.9mm, 9.5±2.4mm and 8.5±3.0mm respectively). The LV sphericity index (diameter/length ratio) was increased in the SLV but not the EA/TVD group (mean±SD SLV 0.67±0.19, EA-R 0.50±0.13, EA-A 0.46±0.08, Control 0.43±0.08; $p<0.001$). Longitudinal velocity and displacement was increased in EA/TVD compared to SLV or Control, but similar in EA-A and EA-R groups. Longitudinal strain to circumferential deformation ratio was increased in the EA-R but not the EA-A or SLV group. Global systolic and diastolic function as assessed by fractional area change, global longitudinal strain, radial shortening index and E/E' ratio were normal in all cases of EA/TVD and SLV.

Conclusion

Despite a similar need for redistribution of flow, EA/TVD show differences to SLV in adaptive mechanics. Most notably, EA/TVD even with retrograde flow do not increase their sphericity and the cardiac output is not augmented through increased circumferential deformation, suggesting preload augmentation may be limited to the longitudinal dimension in EA/TVD.

Funded By:

Abstract #: 105
Presenter: Sabrina Eliason
Supervisor: Cara Dosman
Title: Feasibility of Paediatric Resident Screening Curriculum on Developmental Rotation
Authors: Sabrina Eliason, Debra Andrews, Keith Goulden, Sheila Gallagher, Florencia Ricci, Cara Dosman
Affiliations: University of Alberta
Research Activity: Medical Education: Curriculum Development in Pediatrics
Investigation Type: Qualitative Research

Introduction: Developmental screening is an important skill for paediatric care; however, few residency programs include a formal screening curriculum and there is little published on its practical implementation. We studied the introduction of a new developmental screening curriculum and its effect on resident attitudes and behaviours towards screening instrument use.

Methods: General Pediatric (GenPeds) residents received didactic sessions on using a validated screen, managing positive screens and providing families with information on community resources. They then attended a "Screening Day" during their Developmental Pediatric (DP) rotation in a GenPeds clinic for high volume practice. Residents recorded volume and results on a log sheet. Attitudes about screening were noted during resident interviews and on mid-curriculum surveys.

Results: Over four years (April 2011—December 2014), 41 residents participated and screened a total of 475 children. Mean screens per resident was 14 PEDS (range 3-27). Mean number of PEDS:DM per resident was 2.4 (range 0-9). Resident experiences with the curriculum were overall positive, with improved knowledge of community resources. Feedback led to increased screening opportunities throughout the Program. The main obstacle to screening -- short waiting room time -- resolved with scheduling adjustments.

Conclusions: Integrating screening education into GenPeds residency during the DP rotation was feasible (i.e. residents were able to complete, score and interpret a base number of screens) and highly acceptable to residents. Strong core teaching from DP educators in conjunction with massed practice in community GenPeds clinic was successful in developing a developmental screening curriculum for paediatric residents.

Funded By: Trainee Travel Grant

Abstract #: 106
Presenter: Anne Halpin
Supervisor: Lori West
Title: HLA antibody monitoring in VAD patients: How are we doing?
Authors: Anne Halpin, Simon Urschel, Daniel Kim, Lori West, Trish Campbell, Holger Buchholz, Jennifer Conway
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Transplant
Investigation Type: Quantitative Research

Introduction

Implantation of a ventricular assist device (VAD) has been shown to be a risk factor for development of HLA antibodies. HLA antibodies are known to be associated with poor graft outcomes post-transplant and increase the difficulty of finding a compatible donor. Although the exact role of VADs in the development of antibodies is not yet clearly understood, it is important that patients with VADs are identified to the HLA lab so that relevant samples are tested after this sensitizing event.

Methods

Adult and pediatric patients who received a VAD (pulsatile or continuous flow) between 2005 and 2013 were included. Data were collected from the University of Alberta HLA laboratory's information system and VAD database. A review of the HLA antibody testing performed was completed. The VAD implant dates were confirmed and the samples were categorized as pre- or post- the first implant.

Results

There were 140 patients between 2005-2013 that received a VAD with HLA samples received from 79 adults and 42 pediatric VAD patients. There were 19 patients for whom no samples had been sent to the laboratory. Samples for HLA antibody analysis were sent both pre- and post-VAD in 66% (n=52) of the adult VAD patients. 21% (n=17) of the adult patients had only pre-VAD samples and 13% (n=10) had post-VAD samples only. In the pediatric population, samples were sent both pre- and post-VAD in 83% (n=35) of patients, with one having only pre-VAD samples and 15% (n= 6) only post-VAD samples. The majority of patients from whom no sample was analyzed had been implanted with short-term VADs and were unlikely to have proceeded to transplant; 2 patients with no testing had long-term VADs.

Both the adult and pediatric groups had samples sent without identifying the VAD implant (n=42). Both groups had patients who proceeded to transplant without the laboratory's knowledge of the VAD implantation.

Conclusions

The majority of both pediatric and adult VAD patients in this UofA cohort underwent both pre- and post-VAD testing for HLA antibodies. However, there were a number of patients not identified in the HLA lab as having received a VAD. Consistent collection and appropriate communication with the HLA lab are essential to establish which samples are critical for determining potential treatment options for these critically ill patients, including the risks of heart transplantation following VAD placement. Analysis of the HLA antibody status of the patients included in this study is ongoing.

Funded By:

Abstract #: 107
Presenter: Prasad Ravi
Supervisor: Lida Hornberger
Title: Prenatal Diagnosis of Criss-Cross Heart: Defining Complex Anatomy & Predicting Neonatal Outcomes
Authors: Prasad Ravi, Deborah Fruitman, Lindsay Mills, Timothy Colen, Lisa Hornberger
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Qualitative Research

Introduction: Criss-cross heart (CCH) is a rare congenital heart defect (CHD) found in 8 of 1,000,000 live births. The normal cardiac ventricular inflows run in parallel; whereas, in CCH the ventricular inflows cross superiorly and inferiorly at right angles to each other. With a large spectrum of anatomical and pathophysiological variations, postnatal care may include single ventricle palliation or biventricular repair, but rarely no intervention is necessary. Because of its rarity, only 2 previous case reports describe the prenatal diagnosis of CCH. In the current study, we review our experience with fetal CCH consecutively encountered in our province over the past 5 years to define the presentation, cardiac anatomy, extracardiac pathology and clinical outcomes associated with fetal CCH.

Methods: This study represents a case series. We identified affected pregnancies through our fetal cardiology database. Fetal and postnatal echocardiograms and pre and postnatal clinical records were reviewed.

Results: Of 553 pregnancies with a fetal complex CHD during the study period, 5 had a diagnosis of CCH. Referral for fetal echo was for suspected in CHD in all, and none had significant extracardiac pathology. Detailed methodical 2D and color Doppler fetal echocardiography defined the complex diagnoses which were subsequently confirmed after birth (n=4) or at fetal autopsy (n=1) (Table). In four continued pregnancies, neonatal presentation was correctly predicted.

Case	GA (weeks)	Atrial-Visceral Situs	Segmental anatomy	AV Connection & AV axis	VA Connection	Ventricular arrangement	Additional Cardiac	Outcome
1	32	Normal	{S,L,S}	Concordant, CCW	DORV	Anterior-right LV/posterior - left RV	Small MV/LV, VSD, coarctation	s/p Norwood & Fontan, now 4yrs
2	25	Normal	{S,D,L}	Concordant CW	Discordant	Superior RV	VSD, critical PS, TV override	DTGA, VSD, PS physiology, s/p central shunt, now
3	28	Normal	{S,D,L}	Concordant CW	Discordant	Superior RV	Small VSD	DTGA physiology s/p ASO, now 1yr
4	22	Normal	{S,D,L}	Concordant CW	Discordant	Superior RV	VSD, Smaller TV	TP at 22 weeks
5	23	Normal	{S,L,D}	Discordant CCW	Discordant	Left-Inferior-posterior LV/Right-	VSD, PS, straddling TV	L-TGA physiology, neonate

ASO, arterial switch operation; AV, atrioventricular; CW, clockwise; CCW counterclockwise; GA, gestational age; PS, pulmonary stenosis; TGA, transposition of great arteries; TP, termination of pregnancy; VA, ventriculoarterial; VSD,ventricular septal defect;

Conclusion: Detailed evaluation of the fetal CCH can result in correct anatomical and physiological diagnoses. Prenatal diagnosis of CCH demands a full understanding of the anatomy and physiology to predict presentation at birth as well as to provide accurate prenatal counseling.

Funded By: Not funded

Abstract #: 108
Presenter: Olena Bilyk
Supervisor: Lynne-Marie Postovit
Title: NODAL CONTRIBUTES TO CISPLATIN RESISTANCE IN OVARIAN CANCER CELLS
Authors: Olena Bilyk, Lynne-Marie Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Mixed Methods

Introduction. The capacity of ovarian tumors to grow and propagate is dependent on a small subset of tumor cells, termed cancer stem-like cells, which contribute to drug resistance, and metastasis. Nodal, an embryonic morphogen has been found to sustain stem cell pluripotency and cellular plasticity, but in cancer cells its expression promotes cancer stem cell renewal, tumor growth, invasion, angiogenesis and metastasis. The role of Nodal in the development of recurrent chemoresistant OC has not been previously investigated. The aim of this study was to investigate whether Nodal can modulate resistance of OC cell line A2780s to cisplatin.

Methods. Human OC cell line A2780s was cultured in DMEM/F12 medium supplemented with 10% FBS and treated with cisplatin IC50 dose. Cytotoxity of cisplatin was determined by MTT assay (Roche) and clonogenic assay. Nodal expression after cisplatin treatment was determined by digital PCR and
immunofluorescence staining. To increase Nodal signaling, we used a Nodal expression vector (versus an empty pcDNA3.3 ™ 3.3-TOPO cloning kit; vector; pcDNA
Invitrogen). We also employed recombinant human Nodal (rhNodal; R&D). Transfection was performed with Lipofectamine (Invitrogen) as per manufacture instructions. Cell cycle analysis after cisplatin treatment and expression of cancer stem cell marker CD133 were determined using flow cytometry analysis (FACS). *In vitro* sphere limiting diluting assay was applied to measure ovarian cancer stem cell (OCSC) self-renewal.

Results. The expression of Nodal increased significantly in A2780s cells after 24h cisplatin treatment (20,000 copies/1ug RNA versus 800 copies/1ug RNA in untreated cells) and retained for 96h after cisplatin withdrawal (120,000 copies/1ug RNA). Overexpression of Nodal rendered A2780s cells more resistant to cisplatin (IC50 2.9ug/ml) compared to control cells (IC50 1.3ug/ml). Treatment of A2780s cells with rhNodal (100ng for 24h) during cisplatin treatment increased the ability of ovarian cancer cells to form spheres. Cisplatin along with rhNodal treatment increased the population of CD133 positive cancer stem cells in A2780s cell line (5.85% versus 0,65% in untreated cells and 1.75% after cisplatin treatment alone). Cell cycle analysis revealed that treatment of A2780s cells with rhNodal prevented cell arrest in S phase after cisplatin treatment (19.4% of cells in S phase after rhNodal+cisplatin versus 63.6% - after cisplatin alone).

Conclusion. Our findings demonstrate that Nodal may contribute to cisplatin resistance in OC cells and tumor initiation capacity after drug therapy, and may hold promise as a therapeutic target to prevent chemoresistant recurrence.

Funded By: CIHR

Abstract #: 109
Presenter: Curtis Hodge
Supervisor: Mark Glover
Title: A new way to modulate the BRCA1 DNA repair pathway
Authors: Curtis Hodge, Ross Edwards, Craig Markin, Darin McDonald, Mary Pulvino, Michael Huen, Jiyong Zhao, Leo Spyracopoulos, Michael Hendzel, Mark Glover
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Mixed Methods

Introduction

Ubc13 is an E2 ubiquitin conjugating enzyme that functions in the nuclear BRCA1 DNA damage signaling pathway and cytoplasmic inflammatory NF-kB signalling. Recently, Ubc13 has been shown to participate in breast cancer metastasis. Ubc13 is a critical non-redundant E2 enzyme that functions with multiple other ubiquitination enzymes to create a specific type of ubiquitin signalling chain called lysine 63-linked ubiquitin chains. These ubiquitin chains play important roles in the cellular NF-kB pathway important for the immune and inflammatory response and the BRCA1 DNA damage response pathway to fix DNA double strand breaks.

Methods

We used X-ray crystallography to determine crystal structures of Ubc13 bound to two small-molecule inhibitors as well as a mutant Ubc13 that we designed to resist one of the compounds *in vitro*. Western blotting with an anti-ubiquitin antibody was used to study the *in vitro* ubiquitination inhibition by the two inhibitors. Two stable mammalian cell lines were generated with a retroviral vector to test the specificity of one of the compounds. Immunofluorescent staining of the stable cell lines exposed to ionizing radiation was used as a measure of DNA repair factor recruitment to the sites of DNA double strand breaks.
Immunofluorescence and an enzyme-linked immunosorbent assay was used to measure the proper functioning of the NF-kB pathway.

Results

Here we present the structures of complexes of Ubc13 with two inhibitors, NSC697923 and BAY 11-7082. These inhibitors have been shown to inhibit DNA damage and NF-kB signalling in human cells. NSC697923 and BAY 11-7082 both inhibit Ubc13 by covalent adduct formation through a Michael addition at the Ubc13 active site cysteine. The adducts of both compounds exploit a binding groove unique to Ubc13. We developed a Ubc13 mutant which resists NSC697923 inhibition *in vitro* and in mammalian cells.

Conclusions

Using the NSC697923-resistant Ubc13 mutant, we show that the inhibition of cellular DNA damage and NF-kB signalling by NSC697923 is largely due to specific Ubc13 inhibition. We propose that unique structural features near the Ubc13 active site could provide a basis for the rational development and design of specific Ubc13 inhibitors, which could be used to regulate critical cancer-associated signaling pathways, such as the BRCA1 pathway.

Funded By: AIHS

women & children's health research institute

Abstract #: 110
Presenter: Jiesi Zhou
Supervisor: YangXin Fu
Title: Notch and TGFβ cooperatively regulate EMT in epithelial ovarian cancer cells
Authors: Jiesi Zhou, AbulK Azad, Saket Jain, HaiChuan Yu, Zhihua Xu, Roseline Godbut, YangXin Fu
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Mixed Methods

Introduction

Epithelial-
mesenchymal transition (EMT) plays a critical role in the progression of epithelial ovarian cancer (EOC). EMT promotes metastasis, acquisition of cancer stem cell s and resistance to chemotherapy in EOC. A better understanding of the molecular mechanism that regulates EMT in EOC will help develop novel therapeutic ap proaches to treat this deadly disease. In this study, we investigated the interaction between Notch and transforming growth factor β (TGFβ) signaling in the cont ext of EMT in EOC cells.

Methods

Human ovarian cell line OVCA429 and SKOV3 cells were used in this study. These cells were stably transduced with the intracellular domain of Notch1 (the consti tutively active form of Notch1) or treated with the human recombinant TGFβ1 to activate Notch and TGFβ signaling, respectively. DAPT (γ-
secretase inhibitor IX) and SB431542 (a TβRI inhibitor) were used to inhibit Notch and TGFβ signaling, respectively. Western blotting and quantitative RT- PCR (qRT-PCR) were used to determine the effect of Notch and TGFβ signaling on EMT and gene expression. Cell migration was measured by the wound- healing assay.

Results

Activation of Notch1 induced EMT in EOC cells as demonstrated by downregulation of epithelial marker
E- cadherin and upregulation of mesenchymal markers (Slug and Snail) as well as change of cells to a
more spindle-
like morphology. Notch1 activation increased phosphorylation of Smad2 (downstream effector of TGFβ) in a TGFβ type I receptor-
dependent manner. Indeed, Notch activation increased the expression of TGFβ and TGFβ type I receptor in EOC cells. Interestingly, TGFβ induced the expression of Jagged1 (Notch ligand) and HES1 (Notch target gene), suggesting that TGFβ increases Notch activation in EOC cells. These results suggest that Notch and TGFβ form a reciprocal positive regulatory loop in EOC cells. Furthermore, we found that activation of Notch sustained TGFβ/Smad signaling and was partially require d for TGFβ-
induced EMT in EOC cells. Functionally, combination of activation of Notch1 and TGFβ was more potent in promoting migration of EOC cells than either Notch ac tivation or TGFβ alone.

Conclusion

Our results demonstrate that Notch and TGFβ form a reciprocal positive regulatory loop in EOC cells and cooperatively regulate EMT and migration in EOC cells, suggesting that Notch and TGFβ signaling could be potential therapeutic targets to treat this deadly disease.

Funded By: Summer Studentship

Abstract #: 111
Presenter: Danielle Peters
Supervisor: Jonathan Dennis
Title: Characterization of six novel Stenotrophomonas maltophilia bacteriophages for their use in clinical phage therapy
Authors: Danielle Peters, Jonathan Dennis
Affiliations: University of Alberta
Research Activity: Women's Health : Infection, Inflammation, Immunology
Investigation Type: Mixed Methods

Characterization of six novel *Stenotrophomonas maltophilia* bacteriophages for their use in clinical phage therapy

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Introduction: Cystic fibrosis (CF) is the leading autosomal recessive genetic disorder affecting Caucasians of European decent. Gender differences have been noted in CF individuals, with women facing earlier lung colonization by several pathogenic bacteria[2] and worse clinical outcomes when compared to males[1].
One such CF pathogen is the highly antibiotic resistant bacterium *Stenotrophomonas maltophilia,* which has been shown to be responsible for significant levels of morbidity and mortality in CF individuals. Due to the ineffectiveness of antibiotic therapy on *S. maltophilia* lung infections, we are exploring the possibility of aerosolized bacteriophage (phage) therapy. The first step of using phages in clinical therapy is to characterize the phages through genome sequencing and analyses, ensuring the phages do not contain undesirable genes and are safe for human use.

Methods: Using three clinical *S. maltophilia* strains, six phages were isolated from soil around the Edmonton area. Electron micrographs for each phage were obtained for classification purposes. Restriction fragment length polymorphisms (RFLP) analysis for each phage was conducted using 26 restriction enzymes. Host range analysis was conducted for each phage using 27 clinical *S. maltophilia* isolates from the Provincial Laboratory for Public Health - University of Alberta Hospital. Four phages were sequenced using Illumina technology, while a fifth phage was sequenced using Pacific Biosciences technology. Genome assembly and analysis was completed using CLC Genomics Workbench, SPADES, and Geneious.

Results: We have isolated six bacteriophages specific to clinical strains of *S. maltophilia* from a range of environmental soil samples. Electron micrographs of the six phages allowed morphological classification of the phages to either *Siphoviridae* or *Myoviridae* families of the *Caudovirales* order. Host range analysis of the six phages indicates four phages have broad host ranges, with phages DLP1 and DLP2 exhibiting an extended host range not yet documented in bacteriophages before.

Conclusions: The first step towards obtaining approval for the use of bacteriophages in clinical therapy has been completed through the comprehensive characterization of the six *S. maltophilia*-specific phages. This research is especially relevant to women with cystic fibrosis as these women face earlier lung colonization with CF pathogens, have poorer clinical outcomes and shorter life expectancies.

Funded By: NSERC

women & children's health research institute

Abstract #: 112
Presenter: Michelle Bischoff
Supervisor: Debra Andrews
Title: Academic Milestones: Medical Students' Knowledge of Child Development
Authors: Michelle Bischoff, Peter MacPherson, C. Rebecca North, Debra Andrews
Affiliations: University of Alberta
Research Activity: Child Development, Medical Education
Investigation Type: Quantitative Research

Introduction

Child development is a critical aspect of medical education for which learners commonly report low confidence. This longitudinal study assessed medical students' knowledge of pediatric developmental milestones at four evaluation points in medical school: the start of Year 1, the end of pre-clinical teaching in Year 2, after pediatric clerkship in Year 3, and at the end of medical school. Previously, we reported that students' baseline knowledge of milestones was poor, did not improve significantly after preclinical education, and did improve after clerkship (but remained weak overall). We now report knowledge of milestones at the end of medical school.

Methods

Medical students completed an online nine question survey assessing knowledge of 17 motor and non-motor developmental milestones. 56 students completed the test in both first and fourth year. Changes in students' individual milestone scores between years 1 and 4 were assessed using a paired *t* test. *T* tests were used to analyze mean scores for Year 4 students compared to knowledge of the general population on both motor and non-motor milestones.

Results

Regarding individual student scores between years one and four, knowledge of motor milestones did not improve significantly, while that of non-motor milestones increased a small but statistically significant amount (1.04 points, $p<0.001$). Mean overall milestone scores increased by a small but statistically significant amount (1.28 points, $p<0.001$). Compared with the general population, mean scores for fourth year medical students were 0.03 points higher on motor milestones (NS), 0.96 points higher on non-motor milestones ($p<0.001$), and 0.98 points higher on overall milestones ($p<0.001$).

Conclusions

Our longitudinal study revealed that medical students' knowledge of developmental milestones improved significantly over the four years of medical school. However, graduating students' overall knowledge remained poor compared to what is expected at the physician level. Medical students lack knowledge of child development, a significant aspect of medical education.

Funded By: ACCFCR

women & children's health research institute

Abstract #: 113
Presenter: Linda Mahgoub
Supervisor: Ian Adatia
Title: Pulmonary vein stenosis of prematurity: Epidemiology and survival from a
Authors: Linda Mahgoub, Tarek Kaddoura, Ashok Kakadekar, Frank Dicke, Rebecca Kamney, Ortego Paloma Lopez, Jesus del Cerro Maria, Jeff Fineman, Andrew Reddington, Ian Adatia
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction

Pulmonary vein stenosis (PVS) is a rare often progressive and fatal disease that may not be apparent at birth. Premature birth maybe associated with PVS.

Methods

We undertook a retrospective multi-center cohort study of patients born

prematurely and diagnosed with PVS between 2000-2014. We excluded total

anomalous pulmonary venous drainage, heterotaxy or gestational age

≥37wks. **Results**

We identified 39 patients, 67% were male, median gestational age was 28-weeks (22wks-36wks) and mean birth weight was 1.1kg (433g-2645g). 15 patients (38%) were one of twins whose twin-siblings were unaffected. At diagnosis 72% had developed chronic lung disease (CLD) and 51% were discharged on home oxygen. History of PDA ligation was present in 31% of patients and necrotizing enterocolitis in 23%. 82% of patients underwent echocardiography in the neonatal period without diagnosis of PVS. Median age at PVS diagnosis was 6.5 months (1m-6yrs). Evaluation for pulmonary hypertension in 67% of patients led to a diagnosis of PVS. In 23% of patients PVS was found incidentally. PVS was diagnosed by echocardiography in 56% of patients and contrast CT-angiography, MRI or cardiac catheterization in 44%. Unilateral PVS was found in 64% of patients and 88% of these had a left-side involvement. Management included surgery in 46 %, supportive therapies in 44 % and a palliative approach in 10%. Freedom from death or re-stenosis for all patients was 73% at 1-year and 55% at 2, 5,10 years. PVS diagnosed before 6 months was associated with shorter survival.

Conclusion

PVS in infants who were born prematurely may be unapparent at birth,

associated with pulmonary hypertension, CLD and O2 dependency and is often overlooked by routine echocardiogram. There is a male predisposition and predilection for left sided veins. The occurrence of PVS in one twin suggests that epigenetic factors may be important in the postnatal development or worsening of PVS.

Funded By:

Abstract #: 114
Presenter: Jillian Popel
Supervisor: Catherine Morgan
Title: Neurocognitive outcomes in children with chronic kidney disease requiring dialysis and or renal transplant.
Authors: Jillian Popel, Catherine Morgan , Charlene Robertson , Gwen Alton
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Introduction

Previous studies have suggested children with chronic kidney disease (CKD) are at risk of cognitive, motor, speech and language delays. Few studies, however, have examined development longitudinally in children requiring dialysis or transplant in early childhood. We therefore propose a study evaluating the long-term developmental outcomes of children in Alberta with end-stage renal disease and undergoing dialysis at <12 months of age, or renal transplant <6 years of age. We hypothesize children with CKD requiring dialysis and or renal transplant exhibit developmental delay on age-appropriate psychometric tests of cognition, language, and adaptive skills or neurological impairments (cerebral palsy, epilepsy, and visual or hearing impairments). We also hypothesize that children with CKD-related complications (anemia, frequent hospitalization, impaired early growth, uremia) will be at greater risk of neurodevelopment impairments than children without these factors.

Methods

This prospective, longitudinal, inception cohort study is part of an interprovincial neurodevelopmental follow-up program for children from western Canada who have had complex therapies (Western Canadian Complex Therapies Program (WCCTP)). All children in Alberta requiring dialysis at <12months or renal transplant
< 6 years old are included. Developmental outcome assessments are planned for 4, 6, and 8 years of age.

Results

Data collection is still in progress. Preliminary data of 18 patients showed an average age of dialysis at 6.8 months. Thirteen patients were transplanted (average
age at transplant was 33 months). Nine patients were anemic pre-dialysis and 4 patients at 12 months of age. Average urea and creatinine at start of dialysis was
20.7 mmol/L and 288.1 µmol/L respectively. The average days of hospitalization in the first year of life was 137 days (range 26-305).

Conclusions

Our study will identify specific developmental issues faced by this patient population and will improve the ability of clinicians to have informed discussions regarding the developmental outcomes of young children post-dialysis and post-transplant. This study may identify potential predictors of poor developmental outcomes, generating hypotheses that may be investigated further to improve outcomes of these children.

Funded By: Trainee Research Grant

women & children's health research institute

Abstract #: 115
Presenter: Catherine Corriveau-Bourque
Supervisor: Maria Spavor
Title: SECONDARY MENINGIOMAS IN SURVIVORS OF NON-CENTRAL NERVOUS SYSTEM CHILDHOOD CANCER
Authors: Catherine Corriveau-Bourque, Frank van Landeghem , Natalie Logie, Maureen Disciglio, Susan Chafe, Maria Spavor
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Oncology
Investigation Type: Quantitative Research

Introduction: Secondary meningiomas are a late effect of cranial irradiation administered as treatment for certain childhood cancers.

Methods: A retrospective review was completed of 797 medical records of patients followed in the Childhood Cancer Survivor Program (established 1971) at the Stollery Children's Hospital, Edmonton, Canada, from its inception until July 2013, to establish the incidence, morbidity and risk factors for secondary meningiomas in a population of non-central nervous system (CNS) childhood cancer survivors followed over 40 years at one centre.

Results: Ninety six patients received cranial irradiation for non-CNS neoplasms. Sixteen (16.7%) developed symptomatic meningiomas from 4 to 35 years (median 24 years) after completion of therapy. Fourteen were survivors of acute lymphoblastic leukemia (ALL), 1 of lymphoblastic lymphoma (LBL) and 1 of neuroblastoma. Therapy was initiated in these 16 patients at a median age of 3.5 years (range 0.3-14 years). Of the 96 patients, 69 received cranial irradiation for ALL or LBL. All 15 patients who developed meningiomas in this population had received > 2000 cGy. Meningiomas were not diagnosed in survivors who received <1800 cGy. Fourteen (88%) of patients diagnosed with meningiomas required surgical resection(s). Pathology specimens were reviewed and identified 6 patients with meningioma WHO grade I, 6 atypical meningiomas, 1 choroid meningioma, 1 anaplastic meningioma. The meningiomas infiltrated adjacent tissues in 7 patients. Post-surgical recurrences occurred in 43%. The patients experienced considerable morbidities including 5 patients (31%) with seizures, 2 patients with severe neurocognitive/neurologic sequelae, and 1 patient required a shunt. At study completion, 13% of patients had residual disease.

Conclusion: Secondary meningiomas are a frequent complication of cranial irradiation > 2000cGy in survivors of non-CNS childhood malignancies, especially if treated at a young age. They can cause high morbidity and significantly decrease quality of life. Life-long screening for secondary meningiomas in survivors who received cranial irradiation is essential.

Funded By: Trainee Travel Grant

women & children's health research institute

Abstract #: 116
Presenter: Powel Crosley
Supervisor: Mary Hitt
Title: Combination therapy with two apoptosis inducing agents, PAC-1 and TRAIL, as potential treatment for granulosa cell tumour
Authors: Powel Crosley, Kate Agopsowicz, Michael Weinfeld, Mary Hitt
Affiliations: Other
Research Activity: Women's Health : Oncology
Investigation Type: Quantitative Research

Introduction

Granulosa cell tumour (GCT) is an uncommon form of ovarian cancer, constituting ~5% of ovarian neoplasms. Early stage GCT presents a conundrum – while 5- year survival is >90%, more than 30% of women will experience relapsed disease, and 80% of them will die of disease. To date, advances in understanding the molecular characteristics of GCT have not resulted in improved treatments.

Evasion of apoptosis is one hallmark of cancer. Caspase-3 (CASP3) is at the hub of multiple apoptotic pathways and, when active, contributes to an irreversible cascade of protease activity leading to programmed cell death.

Targeted, small-molecule cancer therapies are drugs designed to interact with the enzymatic activity of proteins affecting tumour growth and progression. As a targeted therapy, they fight cancer cells with more precision and potentially fewer side effects.

Procaspase activating compound-1 (PAC1) is a small-molecule drug which induces activation of CASP3 by sequestering an inhibitory zinc ion, and it has been shown, *in vivo*, to be well-tolerated and effective in the treatment of other cancers.

This study reports on preliminary experiments testing our hypothesis that combining small-molecule PAC1 with drugs affecting the apoptotic pathway will result in increased killing of GCT cells, versus either drug alone, and may represent a novel, more effective therapeutic approach.

Methods

GCT cell line, KGN, was treated *in vitro* with a 6-log range of PAC1 concentrations, for selected time points, to establish a dose-response curve. KGN cells were then treated *in vitro,* as above, with various concentrations of TNF-related apoptosis-inducing ligand (TRAIL) to establish its dose-response curve in KGN. Calculated EC50 values guided selection of concentrations for PAC1 and TRAIL which were applied in various combinations to look for improved efficacy.

Results

Preliminary *in vitro* tests showed 20 µM PAC1 reduces viability in KGN cells, compared to untreated control ($p<0.001$). Likewise, 10 ng/mL TRAIL reduces KGN viability compared to control ($p<0.05$), although PAC1 alone was significantly more effective than TRAIL alone ($p<0.001$).

Combination of 20 µM PAC1 with 10 ng/mL TRAIL produced significant decrease in viability of KGN cells compared to control, PAC1 alone, and TRAIL alone ($p<0.001$).

Conclusions

These *in vitro* results support the hypothesis that combining small-molecule drugs targeting CASP3 in combination with drugs affecting the apoptotic pathway is potentially an effective, novel treatment for GCT that warrants further study.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 117
Presenter: Geetha Venkateswaran
Supervisor: Sujata Persad
Title: Role of β-catenin/Active β-catenin in Osteosarcoma progression
Authors: Geetha Venkateswaran, Linda Xia
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Oncology
Investigation Type: Quantitative Research

Background: Osteosarcoma (OS) is the most common primary bone malignancy with high incidence in children and adolescents. Although the overall survival rate has increased in OS patients over years, it still remains as one of the childhood cancer with lowest overall survival rate. Wnt signaling pathway is one of the signaling pathways that is deregulated in most cancers. Although a number of studies have shown deregulation of this pathway to be implicated in OS, role of β- catenin (key regulatory component of Wnt signaling) in this cancer is not clear. While some studies support the involvement of β-catenin in OS, others show the contrary. All these studies investigate the role of β-catenin rather than Active Beta Catenin (ABC) which is a fraction of β-catenin that is transcriptionally active. ABC transcribes genes involved in cell proliferation, invasiveness and hence promotes cancer. Therefore in our study we are interested in investigating the role of β-cat/ABC in OS progression.

Methods: We used two pairs of cell lines that represents OS progression: Saos2, Saos2-LM7 (aggressive cell line derived from SaOS2), HOS and HOS-143B (aggressive cell line derived from HOS). We used Ezrin, MMP2 and MMP9, some of the currently known markers that are known to be involved in OS progression as measure of aggressiveness in the cell lines used. Western blotting on whole cell lysate and cytoplasmic/nuclear fractions was carried out to determine the cellular levels of β-cat and ABC. We also used Immuno-fluorescence techniques for determining the cellular localization of β-cat and ABC.

Results: Our results showed the aggressive OS cell lines (SaOS2-LM7 and HOS-143B) to express higher cellular levels of ABC compared to their less aggressive parent cell lines SaOS2 and HOS. However there was no significant change in the levels of β-cat with aggressiveness. This observation was consistent with our findings from blots on cytoplasmic/nuclear fraction and immunofluorescence analysis.

Conclusion: Our results suggest no association between β-cat and OS progression, which is in accordance with a few studies in the literature. However we observe a strong association between ABC and OS progression. We therefore propose that ABC might potentially have a role in progression of OS. In future we plan on carrying out experiments to understand the possible mechanism of ABC in OS progression.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 118
Presenter: Zuoqiao Wu
Supervisor: Robert Ingham
Title: The role of JunB transcription factor in the pathobiology of ALK+ ALCL.
Authors: Zuoqiao Wu, Mihye Yang, Julinor Bacani, Robert Ingham
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Oncology
Investigation Type: Quantitative Research

Introduction

Activator Protein-1 (AP-1) family transcription factors regulate many normal cellular activities and their abnormal expression has been associated with various malignancies. My project focuses on the function of the AP-1 transcription factor, JunB, in the T cell lymphoma, Anaplastic Lymphoma Kinase-positive, Anaplastic Large Cell Lymphoma (ALK+ ALCL), where JunB is highly expressed.

Methods and Results

To investigate the function of JunB in the pathobiology of this lymphoma, we generated stable knock-downs of JunB with shRNAs and examined their effect on cell growth. We found that JunB is essential for the tumour cell proliferation because JunB knock-down resulted in a decreased proliferation rate; however, we observed no effect on apoptosis in the JunB knock-down cells. To further investigate JunB function in ALK+ ALCL, we performed microarray experiments comparing the JunB knockdown cells and control cells. Many genes identified in JunB knockdown cells are genes characterize ALK+ ALCL from normal T, suggesting JunB contribute to the transcriptional profile of ALK+ ALCL. Gene ontology analysis of our microarray data suggests that JunB may participate in immune evasion in this lymphoma, given that ~20% of the genes with altered expression in the JunB knock-down cells were related to natural killer (NK) cell- mediated cytotoxicity. In support of this notion, preliminary results demonstrated that JunB knock-down cells are more vulnerable to NK cell-mediated killing than cells expressing control shRNA.

Conclusion

In summary, we show that JunB promotes tumour cell proliferation, influences the expression of genes that characterize this lymphoma, and protects tumour cells from immune surveillance.

Funded By: ACF

Abstract #: 119
Presenter: Ning Yang
Supervisor: Ing Swie Goping
Title: Characterization of cell death induced by the cyanine dye D112: a potentially selective anti-cancer compound
Authors: Ning Yang, Paul Gilman , Razmik Mirzayans , Xuejun Sun, Nicolas Touret , Michael Weinfeld, Ing Swie Goping
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Qualitative Research

Introduction

While cancer becomes the leading cause of death in Canada, the anticancer drug discovery is decelerated by the low selectivity and low efficiency to solid tumors. Novel compounds with higher discrimination for cancer cells, especially in solid cancer, are still in need. In the 1970's, Kodak Laboratories initiated a screen of approximately 7000 dye structural variants for selective toxicity to cancer cells. Among these, cyanine dye D112 was identified as a promising compound with elevated toxicity against a colon cancer cell line in comparison to a non-transformed cell line.

Methods

We used a cell-based approach, combining with yeast animal model, to investigate the effect of D112 on human cancer cells as well as yeast strains.

Results

In our study, D112 induced apoptosis in the T-cell leukemia cell line (Jurkat). Importantly, D112-induced apoptosis was inhibited by elevated expression of Bcl-2 or deficient expression of BAX/BAK. D112 accumulation in mitochondria further implicate that mitochondrial dysfunction plays a vital role in D112-induced apoptosis. In addition, D112 can significantly induce cell death in cell lines derived from solid tumors, while the non-transformed cell lines show resistance.
Insights into the molecular mechanism of D112 action discovered that D112 caused ROS production. Considering cellular stress induced ROS in cancer cells makes them less tolerance to further ROS generation, it is possible that ROS production contributes to D112 selective toxicity. Interestingly, in yeast model, petite mutants (respiratory deficient) showed resistance to D112 cytotoxicity, indicating that a functioning respiration chain and/or mitochondrial DNA is important for D112 action.

Conclusions

In summary, D112 mitochondria / apoptosis targeting property may distinguish it from other common anti-cancer agents as a potential drug warranting further investigation.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 120
Presenter: Lesley Brennan
Supervisor: Irena Buka
Title: Children's Environmental Health Clinic (ChEHC): A three year summary of patient data
Authors: Lesley Brennan, Alvaro Osornio-Vargas, Alexander Doroshenko, Jamal Tarrabain, Harold Hoffman, Donald Spady, Irena Buka
Affiliations: Covenant Health
Research Activity: Children's Health - Environmental Exposures
Investigation Type: Quantitative Research

Introduction

The Children's Environmental Health Clinic (ChEHC) is dedicated to understanding and managing child health concerns associated with environmental exposures (chemical, biological, physical and social). This unique program includes clinical, research, and educational components. Our clinical program is located at the Child Health Clinic at the Misericordia site, where we see patients with a wide variety of health complaints and exposures. Our goal is to summarize patient characteristics over the past three years (2012-2014) in order to guide the development of much needed educational resources and research. Our objective is to conduct descriptive statistics on patient health concerns, potential exposures, and demographics.

Methods

Extensive patient information is collected through the use of a Paediatric Environmental Health History questionnaire (PEHH), which consists of over 150 questions in 9 sections including demographics, general environment, school environment, daycare/day home environment, lifestyle, prenatal exposures, infancy diet, respiratory symptoms, and neurodevelopmental symptoms. Clinical environmental data for all ChEHC patients between 2012-214 were compiled in an Excel database. Referral sources, patient demographics, health issues and exposures were summarized.

Results

The yearly number of patients referred to ChEHC increased from 12 in 2012 to 45 in 2014. Children are typically referred by paediatricians and family physicians. Our patient population is predominantly male (60%), age 10 or younger (81%), and living in the greater Edmonton area (64%). Approximately 22% were from rural Alberta. Most were seen in our clinic (80%), a smaller proportion were consulted by Telehealth (13%), and telephone (7%). While children frequently presented with more than one health concern (22%), asthma/respiratory issues were commonest (67%) followed by neurodevelopmental issues (22%).
Exposures most frequently considered were: indoor air (e.g. tobacco smoke, mold, dust, carbon monoxide), outdoor air (e.g. traffic/industry pollution), and lead toxicity. Less common exposures include pesticides, asbestos, cannabis smoke and cultivation, food dyes and additives, and radon.

Conclusions

Our results demonstrate a growing need for clinical services in Paediatric environmental health. Several health concerns and potential exposures per child are common. Respiratory issues and indoor/outdoor air pollution represent the main concerns, and will be reflected in future educational and research activities. Less common issues and exposures require special attention and resources to help fill gaps in knowledge.

Funded By: Covenant Health

women & children's health research institute

Abstract #: 121
Presenter: Michele Dyson (Hamm)
Supervisor:
Title: The prevalence and impact of cyberbullying on children and young people: a scoping review of social media studies
Authors: Michele Hamm, Amanda Newton, Annabritt Chisholm, Jocelyn Shulhan, Andrea Milne, Purnima Sundar, Heather Ennis, Shannon Scott, Lisa Hartling
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Introduction: Social media use is highly prevalent among children and youth and drives many of their interactions. While there are many benefits to the use of social media, there are also potential harms, including those posed by cyberbullying. Our objective was to conduct a scoping review of the health-related effects of cyberbullying via social media among children and youth.

Methods: We searched 10 electronic databases in January 2012, and updated our search in June 2014. We included studies reporting primary research that described or evaluated the use of a social media tool in the context of cyberbullying, and were conducted with children or youth. All included studies were assessed for methodological quality using the Mixed Methods Appraisal Tool. Heterogeneity in study objectives and outcomes precluded the pooling of results; therefore a narrative analysis was conducted.

Results: We included 36 studies, most of which were conducted in the United States (58.3%) and included middle and high school populations (66.7%) aged 12- 18 years (97.2%). There was a wide range in the reported prevalence of cyberbullying, with a median of 23.0% (interquartile range 11.0% to 42.6%). Five studies evaluated the relationship between cyberbullying and anxiety, and five studies investigated self-harm or suicidality, and all found inconsistent and/or weak correlations. A statistically significant association between cyberbullying and depression was reported in ten studies. The most commonly reported reasons for cyberbullying were due to relationship issues, and girls were most often the victims. Most children and youth responded passively to incidents of cyberbullying, and there was a pervasive lack of awareness or confidence that anything could be done about it.

Conclusions: The results of this review will provide important information characterizing cyberbullying via social media, and will inform the development of effective prevention and management strategies.

Funded By: CIHR

women & children's health research institute

Abstract #: 122
Presenter: Winnona Rea
Supervisor: Khalid Aziz
Title: Improving sentinel event reporting in neonatal intensive care
Authors: Winnona Rea, Khalid Aziz
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Introduction: A sentinel event (SE) is an "unexpected occurrence involving death or serious physical injury…or risk thereof" (Joint Commission 2012). Quality improvement (QI) efforts in neonatal intensive care units (NICU) have targeted babies with SEs such as preterm brain injury (PBI) or retinopathy of prematurity (ROP). QI domains include "evidence", "context", and "facilitation" (Kitson 2008), integrating data collection, local teams, and implementation – a process shown to be effective in the Canadian EPIQ study (Lee 2015). Question: Can we develop an effective SE reporting process that collects data and engages NICU teams? Methods: Using a prospective formative research design, we joined QI teams to evaluate their processes. The focus was on two SEs: PBI and ROP. Through an iterative process, the SE reporting system at Royal Alexandra Hospital (RAH) NICU was evaluated, deconstructed, mapped and reconstructed to meet the needs of babies, QI teams, and frontline staff. Results: RAH NICU supports all 3 QI domains: SE data for preterm babies, available in an annual report; QI teams for both PBI and ROP; and NICU staff education. SE reporting by head nurse began in May 2015, identifying approximately 2 cases of PBI monthly. A process map revealed significant gaps, including: unclear diagnostic criteria; delays in identification and reporting; inability to modify SEs once they had occurred; and exclusion of the clinical team from QI processes. The following changes were recommended: 1) A SE reporting tool with 3 types of events: processes, triggers, and SEs. 2) Collaboration with radiologists and ophthalmologists for SE definitions. 3) Identification of strategies to address processes and triggers. Conclusion: Using formative evaluation, we worked with QI teams, mapped processes, identified gaps, and developed practical tools that would engage frontline staff.

Funded By: Summer Studentship

Abstract #: 123
Presenter: Shannon Scott
Supervisor:
Title: Process evaluations of knowledge translation intervention studies – a systematic review.
Authors: Shannon Scott, Thomas Rotter, Katherine Bannar-Martin, Rachel Flynn, Thane Chambers, Lisa Hartling
Affiliations: University of Alberta
Research Activity: Knowledge Translation
Investigation Type: Mixed Methods

Introduction: Experimental designs for evaluating knowledge translation (KT) interventions for professional behavior change can provide strong estimates of intervention effectiveness but offer limited insight into *how* the intervention worked or was moderated. Consequently, researchers have started exploring the *causal mechanisms* in KT intervention studies through process evaluations, yet there are no methodological standards to guide their design. This study synthesizes current evidence of KT process evaluations to provide methodological recommendations.

Methods: Peer-reviewed search strategies were developed. Studies had to be in English, published since 1996, and were not excluded based on design. A single reviewer screened all titles and abstracts, and studies had to: (1) be a process evaluation of a KT intervention study in health; (2) be a primary research study; and (3) include a licensed health care professional (HCP) providing or receiving the intervention. A second reviewer screened a random sample with 94% inter- rater reliability. Data on study design, data collection details, theoretical influences, approaches to evaluate the KT intervention dose and fidelity, analysis, and outcomes were extracted by two reviewers. Extracted data was analyzed by study design, study quality, and KT intervention. Methodological quality was assessed with a mixed-method scoring tool (MMAT).

Results: Of the 9690 articles screened, 151 studies fit our inclusion criteria. Most process evaluations evaluated barriers, facilitators and/or satisfaction with the KT intervention using qualitative forms of data collection (49.0%), and individual interviews were the predominant method. 80.1% of process evaluations were stand-alone evaluations, not directly accompanying the KT intervention evaluation. Consequently, most process evaluation data was collected post-intervention (50.3%), but specific timing varied widely. Despite the large number of process evaluation articles in this review, only 29.8% were informed by theory, of which the Rogers Diffusion of Innovation Theory was used in 20% of studies. Furthermore, 53.6% of studies had a MMAT score of 50 or less indicating poor methodological quality.

Conclusions: There is widespread acceptance that the generalizability of quantitative trials of KT interventions would be significantly enhanced through *complementary* process evaluations.However, this systematic review found that process evaluations are of mixed to poor quality, and few were guided by theory. Furthermore, most data collection occurred post-intervention undermining the ability to evaluate the *process* of implementation. Strong science and methodological guidance is therefore needed to underpin and guide the design and execution of process evaluations in KT science.

Funded By:

women & children's health research institute

Abstract #: 124
Presenter: Roger Turnell
Supervisor:
Title: Ethiopia-Canada Project: Protecting pregnant/delivering mothers and newborns: Systems approach to strengthening skilled birth attendance and referral
Authors: Roger Turnell, Khalid Aziz, Jill Konkin, Fraser Brenneis, Janet Summerhayes, Amy Fowler, Pam Nordstrom, David Zakus, Abrham Getachew, Wuletaw Chane
Affiliations: University of Alberta
Research Activity: International Medical Education on MNCH
Investigation Type: Qualitative Research

Rationale: The 2011 Ethiopian Demographic and Health Survey indicates the MMR was 676:100000 live births compared to 12:100000 in Canada. The majority of pregnant and delivering mothers live in rural areas and for social, demographic and cultural reasons, do not have access to skilled birth attendants or emergency referral systems. Even with the increased number of midwifery graduates over the last ten years, the clinical skills of graduates are weak and they have little practical experience with normal and high risk deliveries. Our project seeks to address this gap by training Senior Midwife Tutor Trainers [SMTT] and by strengthening the maternal referral system infrastructure. Objectives: Two main goals are to improve midwifery training systems by increasing the clinical skills and pedagogical development of graduating and graduate midwives and to improve the emergency care referral system for pregnant and delivering mothers in order to reduce maternal and neonatal mortality.

Methods: A project directed by the University of Alberta consisting, in part, of a core curriculum based on adult education principles developed by Mount Royal University, University of Alberta and Saint Paul's Hospital Millennium Medical School, Addis Ababa, Ethiopia, assesses learners and institutions, with reinforcement of core midwifery content, routine obstetric care, acute obstetric emergencies, neonatal resuscitation [Helping Babies Breathe] and essential newborn care. Training in management of educational programmes and learners, community assessment, research and evaluation of midwifery practice was provided. This 4 year programme commenced in 2014 and provides five months of classroom, practical field experience and hands-on clinical refresher training.

Results: Forty-two SMTTs from all over Ethiopia have so far graduated. Of 18 SMTTs who graduated in 2014, four have gone on to graduate school in MPH Programs and as of November 2014, fourteen SMTTs reported cascading their training to at least 30 midwifery tutor/teacher colleagues and 150 midwifery students. Twenty-six graduates are just returning to their home institutions to cascade their learning. Currently 14 MNCH research projects are being undertaken.

Discussion: This sandwich type of education and cascading of classroom instruction, field experience, skills refresher in active clinical settings, followed by field experience and return to the classroom for confirmation of learning is an effective adult education method for ensuring quality trained SMTTs. Conclusion: It is anticipated that over the remaining two years and with the production of SMTTs and country saturation that our project will have a significant impact on the reduction of maternal and neonatal mortality.

Funded By: Department of Foreign Affairs and Development [Formerly CIDA}

Abstract #: 125
Presenter: Marina James
Supervisor: Margie Davenport
Title: Neurovascular coupling in healthy pregnancy.
Authors: Marina James, Paige Wakefield, Christina MacKay, Rachel Skow, Craig Steinback, Margie Davenport
Affiliations: University of Alberta
Research Activity: Maternal Research : Cerebrovascular Regulation
Investigation Type: Quantitative Research

Introduction. Neurovascular coupling describes the functional hyperemia which occurs in response to increases in local neural activity. Vascular reactivity is increased in pregnancy; however, the impact of pregnancy on neurovascular coupling has not been described. We hypothesized that the visually evoked cerebral blood flow response would be higher in pregnancy. *Methods*. Nine women in their third trimester of pregnancy (Age = 30 ± 4 yrs, Pre-pregnancy BMI = 23.3 ± 2.0kg/m^2) and nine non-pregnant controls in the early follicular phase of their menstrual cycle (28 ± 7 years, 25.2 ± 3.9kg/m^2) underwent a visual stimulation test. Beat-by-beat mean arterial pressure (MAP) was derived using photoplethysmography (Finometer) and posterior cerebral artery blood flow velocity (PCAVP) was measured using transcranial Doppler ultrasound (Multigon). Percent change in PCAVP and PCA conductance (%PCAVP/MAP) in response to visual stimulation were assessed. *Results***.** At rest, MAP (Non-pregnant: 86.8 ± 7.4mmHg, Pregnant: 87.4 ± 9.6mmHg, p=0.79), posterior cerebral artery blood flow (Non-pregnant: 36.6 ± 5.7cm/s; Pregnant: 34.5 ±8.2cm/s, p=0.56) were similar between pregnant and non-pregnant women. Further, the magnitude (Non- pregnant: 26.5 ± 3.4%, Pregnant: 28.1 ±11.3%, p=0.70) and timing (Non-pregnant: 11.8 ± 2.0s, Pregnant: 11.1 ± 3.9s, p=0.68) of the cerebral blood flow response to visual stimulation was similar during pregnancy. There remained no difference when the response was measured with respect to a change in conductance (Non-pregnant: 26.7 ± 3.2au, Pregnant: 26.7 ± 9.2au). *Conclusions.*These data suggest that in contrast with our hypothesis, neurovascular coupling in pregnant women, assessed by visual stimulation, is similar to non-pregnant women.

Funded By:

women & children's health research institute

Abstract #: 126
Presenter: Liane Kang
Supervisor: Anita Kozyrskyj
Title: The influence of fetal sex on glucocorticoid levels in maternal and cord blood
Authors: Liane Kang, Anita Kozyrskyj, Nicole Letourneau, Katherine Wynne-Edwards, Henry Ntanda, Gerald Giesbrecht
Affiliations: University of Alberta
Research Activity: Maternal Research : Fetal Origins of Adult Disease
Investigation Type: Quantitative Research

Introduction

Measuring glucocorticoids in maternal blood pre-delivery and venous cord blood retrieved at birth is a valid marker of fetal exposure. Cortisol and corticosterone are glucocorticoids which are secreted regularly, and especially in response to stress. 11-beta-hydroxysteroid dehydrogenase is an enzyme working at the placenta that converts cortisol into inactive cortisone; the cortisone to cortisol ratio shows how well cortisol is metabolized. Despite partial blockade, glucocorticoids do cross the placenta and hence changes in maternal glucocorticoid concentrations and/or adjustments in placental 11-beta- hydroxysteroid dehydrogenase activity have the potential to affect the fetus. The aim of this study is to investigate the differences in stress markers in maternal blood before delivery and in cord blood due to fetal sex.

Methods

Data was obtained from the Fetal Programming of Infant Stress Reactivity and Infant Atopic Disease study in the APrON (Alberta Pregnancy Outcomes and Nutrition) general population cohort, where maternal and cord blood were collected at birth. The delivering physician was advised to collect 1mL of cord blood by venus needle aspiration before the severing of the umbilical cord and to collect 1mL of maternal blood. Blood samples were refrigerated and centrifuged within 24 hours. The centrifuged samples were stored frozen at -10°C until pick-up by study personnel. After thawing, serum samples were diluted with zinc sulfate solution, vortexed, incubated at -20°C for 15 minutes and centrifuged. The supernatant was removed for the measurement of cortisol and cortisone levels by an AB SCIEX QTRAP 5500 mass spectrometer. One-sided and two-sided t-tests were conducted to find statistically significant difference between male and female fetuses.

Results

32 newborns were investigated in this study, of which 59% were female. Mean cord serum cortisol was significantly higher ($t = 2.12$, $p = 0.04$) in female newborns (58.8, SD 44.4ng/mL) than male newborns (29.9, SD 24.3ng/mL). Cord corticosterone levels were also significantly higher in female newborns ($t = 2.45$, $p = 0.02$). Maternal blood cortisol, corticosterone, cortisone, and the cortisone to cortisol ratio had no statistically significant differences between the gender groups, although there was a trend for higher cortisol and corticosterone levels in mothers that delivered a female.

Conclusion

In conclusion, the quantification of glucocorticoids in venous cord blood shows sex differences which suggest that the female and male placenta allows different amounts of cortisol to pass through the fetus. Follow-up work will determine whether important covariates such as delivery mode, gestational age at delivery, and birthweight are related to these outcomes.

Funded By: AllerGen NCE

women & children's health research institute

Abstract #: 127
Presenter: Stewart R. Rowe
Supervisor: Dr. Sandra Davidge
Title: Effects of Placental-Derived Microparticles on Vascular Endothelial Cell Function
Authors: Stewart Rowe, Floor Spaans, Anita Quon, Jude S. Morton
Affiliations: University of Alberta
Research Activity: Maternal Research : Preeclampsia
Investigation Type: Quantitative Research

Introduction: Preeclampsia is a pregnancy condition characterized by new-onset hypertension and proteinuria after 20 weeks of gestation. A central feature in the pathophysiology of PE is abnormal placentation resulting in oxidative stress and the release of circulating factors that contribute to vascular endothelial dysfunction. One of the released circulating factors is placenta-specific syncytiotrophoblast-derived microparticles (STBMs). STBMs are heterogeneous cell fragments that are released during normal pregnancy, but are released in increasing amounts in women with preeclampsia. The lectin-like oxidized low-density lipoprotein-1 receptor (LOX-1) is a multi-ligand scavenger receptor activated by multiple ligands such as oxLDL and platelets. Our laboratory has recently shown that LOX-1 expression is increased in vessels of women with preeclampsia and activation of LOX-1 can affect vascular function via superoxide generation. We hypothesize that STBMs may be a potential LOX-1 ligand contributing to endothelial cell dysfunction in preeclampsia.

Methods: Human umbilical vein endothelial cells (HUVECs) were isolated from umbillical cords of healthy pregnant women. HUVEC cultures were incubated in the absence (control) or presence of STBMs (50-200 µg/ml), with or without LOX-1 blocking antibodies. LOX-1 expression was measured using Western blot after 24hrs of stimulation. DHE staining was used to measure superoxide levels after 30 minutes of stimulation as an indicator of oxidative stress. LOX-1 activation has also been shown to lead to ERK1/2 phosphorylation. Therefore, phosphorylated ERK1/2 (pERK1/2) was used as a marker of intracellular activation and was measured after 10 and 20 minutres of stimulation using Western blots.

Results: There were no changes in LOX-1 expression after STBM treatment. STBM treated HUVECs tended to generate higher levels of superoxide (24.9±8.2% increase), however, this was not reduced by adding LOX-1 blocking antibodies. In addition, stimulation with STBMs induced an increase in pERK expression after both 10 (149±68.4% increase in pERK1 and 86.2±25.1% increase in pERK2) and 20 minutes (62.3±12.4% increase in pERK1 and 51.7±9.2% increase in pERK2) indicating cellular activation. However, ERK phosphorylation was also unaffected by LOX-1 blocking antibodies.

Conclusions: STBMs were shown to activate endothelial cells but this seemed to be independent of the LOX-1 receptor. The effects may thus be mediated by other pathways activated by STBMs that require further investigation. Elevated concentrations of circulating STBMs in women with preeclampsia can activate endothelial cells and this may contribute to endothelial dysfunction. These results increase our understanding of endothelial dysfunction in preeclampsia, which is necessary in order to develop therapeutic strategies in the future.

Funded By: Summer Studentship

Abstract #: 128
Presenter: Rebecca Rubuliak
Supervisor: Margie Davenport
Title: Physical Activity, Sedentary Behaviour, and Weight Gain During Pregnancy.
Authors: Rebecca Rubuliak, Charlotte Usselman , Rshmi Khurana, Radha Chari, Maureen Devolin, Michael Stickland, Sandra Davidge, Craig Steinback, Margie Davenport
Affiliations: University of Alberta
Research Activity: Maternal Health - Weight Gain
Investigation Type: Quantitative Research

[1]Program for Pregnancy and Postpartum Health, Physical Activity and Diabetes Laboratory, Faculty of Physical Education and [2]Recreation, Women and Children's Health Research Institute, [3]Alberta Diabetes Institute, [4]Department of Medicine, [5]Department of Obstetrics and Gynecology, University of [6]Alberta, Alberta Health Services.

Research suggests that physical activity (PA) reduces excessive gestational weight gain, which improves pregnancy outcomes and the future health of both mother and infant. However, the independent influence of sedentary behaviour on gestational weight gain is unknown. The study examined the relationship between physical activity, sedentary behaviour, and weight gain during pregnancy. We hypothesized that increased physical activity and decreased sedentary behaviour would independently reduce excessive gestational weight gain. Twenty-six women (30.6±3.6 yrs, 32 ± 3 weeks) with a pre-pregnancy Body Mass Index (BMI) of 24.8±7.2 kg/ wore Actigraph® accelerometers (valid day > 600 mins) in their third trimester for an average of 6.4±1.1 days. Gestational weight gain was measured at the beginning of accelerometer data collection minus self-reported weight immediately before pregnancy. Using the Canadian Society for Exercise Physiology's PA guidelines, women were classified as either meeting or not meeting the recommended 150 minutes of moderate to vigorous PA (MVPA) per week. A partial correlation controlling for pre-pregnancy BMI and week of gestation examined the independent influences of MVPA and sedentary behaviour on gestational weight gain. There were no differences in pre-pregnancy BMI, weeks gestation, or age between groups. Women that met the weekly PA recommendations spent 68.4±7.0% of their day sedentary and 4.6±1.7% doing MVPA. Women that did not meet physical activity recommendations tended to be more sedentary (75.16±9.8%, p=0.08) and accumulated less MVPA (1.1±0.7%, p<0.001). Those that met the weekly PA recommendations gained an average of 10.1±4.4 kg and those that did not meet the recommendations gained an average of 12.1±4.1 kg. Across all women, after controlling for pre-pregnancy BMI and weeks gestation, MVPA was negatively correlated to gestational weight gain (r=-0.551, p=0.005), while sedentary behaviour was not (r=0.260, p=0.20).
Gestational weight gain is modified by MVPA but not sedentary behavior, suggesting a minimum threshold of physical activity is required in order to limit gestational weight gain.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 129
Presenter: Floor Spaans
Supervisor: Sandra Davidge
Title: Syncytiotrophoblast Microparticles Decrease Endothelium-Dependent Vasodilation in Rat Uterine Arteries
Authors: Floor Spaans, Anita Quon, Jude Morton, Sandra Davidge
Affiliations: University of Alberta
Research Activity: Maternal Research : Preeclampsia
Investigation Type: Quantitative Research

Introduction: Preeclampsia is a pregnancy condition characterized by the development of hypertension and proteinuria in the second half of pregnancy. The exact pathophysiology is still unknown but the symptoms appear to be due to the release of placental factors leading to endothelial dysfunction in the mother. One of these factors is syncytiotrophoblast microparticles (STBMs). STBMs are released by the placenta during normal pregnancy and are increased in preeclamptic women. The lectin-like oxidized LDL receptor-1 (LOX-1) is a scavenger receptor that is increasingly expressed in vessels from preeclamptic women and is activated by multiple ligands such as oxLDL and platelets. Activation of LOX-1 can affect vascular function via superoxide generation. We hypothesized that STBMs can activate LOX-1 and contribute to vascular dysfunction in preeclampsia.

Methods: Uterine arteries were obtained from normal pregnant rats at GD20. Vessels were incubated for 24hrs (i) without stimuli, (ii) with STBMs, or (iii) with STBMs together with an LOX-1 blocking antibody. Using wire myography, endothelium dependent vasodilation responses to methylcholine (MCh) were measured. To check for the involvement of superoxide production, MCh responses were assessed in the presence or absence of the superoxide scavenger superoxide dismutase (SOD). In addition, uterine arteries were similarly incubated with STBMs for 24hrs and were snap frozen, sectioned (9 µm) and stained for the presence of superoxide using dihydroethidium staining.

Results: Incubation of uterine arteries with STBMs for 24hrs decreased MCh induced vasodilation at the highest concentrations (42.9±6.8% versus 73.1±3.4% in controls at 10^{-5} M). This was not observed after incubation with both STBMs and the LOX-1 blocking antibody (10^{-5} M). Adding SOD did not significantly improve MCh induced vasodilation (73.4±6.7% at 10^{-5} M) in the STBM incubated vessels. No changes in superoxide production were observed in uterine artery sections.

Conclusions: STBMs disturbed vascular function in uterine arteries, via a LOX-1-dependent pathway. However, this appeared not to be associated with increased superoxide generation after 24hrs of incubation. It is possible, therefore, that another LOX-1-activated signalling pathway may be involved or superoxide was generated at earlier stages and resolved by 24hrs; these aspects await further investigation. These data suggest that higher concentrations of circulating STBMs in preeclampsia can affect vasodilation via activation of the LOX-1 receptor. This may contribute to the development of hypertension in these women. These results increase our understanding of endothelial dysfunction in preeclampsia, which is necessary in order to develop therapeutic strategies in the future.

Funded By: AIHS

Abstract #: 130
Presenter: Nanlin Yin
Supervisor: David Olson
Title: Activated Chemokines at Maternal-Fetal Interface Associate with Parturation
Authors: Nanlin Yin, Xin Fang
Affiliations: University of Alberta
Research Activity: Maternal Research : Infection, Inflammation, Immunology
Investigation Type: Qualitative Research

Introduction

Every delivery is preceded by a massive invasion of circulating leukocytes into the uterine tissues that leads to uterine transformation from pregnancy to labour. Infiltrated leukocytes respond to chemokine signals from human fetal membrane (hfm) cells to regulate inflammatory mediators thereby initiating and amplifying the labour cascade. However, the specific chemoattractant(s) that activates and attracts these leukocytes has not been clarified. Our objective was to identify the chemokine(s) from hfm (maternal-fetal interface) at term not in labour labour (TNL) and term in labour (TL).

Methods

Whole fetal membrane (amnion, chorion and decidua) homogenate mixture (n=3) from TNL and TL groups were subjected to a Proteome Profiler to screen chemokines. RT-PCR and Multiplex separately validated the output of these chemokine candidates at the mRNA and protein levels. Candidate chemokines were applied to the leukocyte migration assay (LMA) to confirm their chemotactic properties.

Results

Proteome Profiler results identified 5 chemokine candidates based upon their degree of expression. RT-PCR confirmed the output of CXCL1 and CXCL8 mRNA were significantly elevated in TL group compared to TNL group ($P < 0.05$) whereas CXCL10, CCL2 and CCL21 were similar and did not reach significance ($P > 0.05$). Multiplex validated CXCL1 was increased at TL than TNL whereas CXCL8 was similar and did not reach significance ($P < 0.05$, $P > 0.05$). The LMA bioassay results indicated all except CCL21 displayed chemotaxis activity. CXCL8 and CXCL1 had the most activity, respectively ($P < 0.001$, $P < 0.01$).

Conclusions

CCL2, CCL21, CXCL1, CXCL8 and CXCL10 might play different roles at the maternal-fetal interface attracting peripheral leukocytes to initiate or maintain labour. CXCL8 and CXCL1 are the most abundant and have the most chemotactic activity. These data provide compelling evidence that chemokines from the maternal-fetal interface regulate leukocyte infiltration during labour. Therefore, these chemokines may be attractive diagnostics or therapeutic targets for preterm birth.

Acknowledgements: Women's and Children's Health Research Institute (WCHRI); Chongqing Medical University; CIHR.

Funded By: Trainee Travel Grant

Abstract #: 131
Presenter: Kaley Donaldson
Supervisor: Sue Ross
Title: Experience of Menopause in Women with Inflammatory Bowel Diseases
Authors: Kaley Donaldson, Vivian Huang, Sue Ross, Beate Sydora
Affiliations: University of Alberta
Research Activity: Women's Health : Mature Women's Health
Investigation Type: Quantitative Research

Introduction

Inflammatory Bowel Diseases (IBD) are debilitating, chronic intestinal disorders usually requiring extensive medical intervention. Menopause is a natural stage in a woman's aging process defined by the end of menstruation and frequently associated with a variety of physical and psychological symptoms due to hormonal changes. Symptoms can be influenced by medical treatment, diet and lifestyle. It is not known whether and how IBD and its treatment affects menopause; neither is it clear how menopause affect the clinical presentation of IBD. The objective of this pilot project was to study the interaction between menopause and clinical presentation of IBD.

Methods

Women age 30 - 65 with IBD were recruited from the Zeidler IBD clinic. Women completed a survey regarding their obstetric and medical history and medication use. Menopause experience was explored using the validated menopause-specific quality of life (MENQOL) questionnaire which uses 29 items in 4 categories (vasomotor, psychosocial, physical, sexual) to assess how much a women is bothered by menopause symptoms on a scale from 1 (symptom not experienced) to 8 (extremely bothered by symptom).

Results

Seventy-one women were recruited comprising women in pre-menopausal (25), peri-, (15), and post-menopausal (31) stage. IBD onset at a young age correlated
with early menopause (R^2 linear = 0.438). The average age of final menstruation in postmenopausal IBD patients excluding those with surgical menopause was
low (44.2 ± 7.9 years) with a median of 46.6 compared to the median age of natural menopause for North American females (51.4). MENQOL scores for the psychological, physical, and sexual categories were significantly higher in post-menopausal women with active disease (5.0±1.7, 5.5±1.0, 6.8±0.8) compared to those in remission (2.6±1.4, 3.7±1.5, 2.8±1.8). Disease activity appeared not to impact vasomotor symptoms including hot flashes and night sweats (4.4±2.4 for women with flares versus 4.3.7±2.4 for women in remission).

Conclusion

Our data demonstrate an effect of IBD onset and severity on the age of menopause onset and symptom perception. The limited number of patients in this pilot project did not allow for a statistically sound analysis to take all confounders into account such as medical history, medications, and life style options. Future studies with higher enrolment numbers will address these confounders. Knowledge gained from this study ultimately will support women with IBD in health choices when coping with hormonal changes and symptoms during menopause.

Funded By: Summer Studentship

Abstract #: 132
Presenter: Annick Poirier
Supervisor: Sue Ross
Title: What are the clinical factors associated with attendance at a multidisciplinary perineal clinic among patients with OASIS?
Authors: Annick Poirier, Sue Ross, Momoe Hyakutake, Debra Slade, Cathy Flood, Jane Schulz
Affiliations: University of Alberta
Research Activity: Women's Health : Urology/Gynecology
Investigation Type: Quantitative Research

Introduction

Obstetrical trauma during childbirth is common and has been identified as a risk factor for development of pelvic floor dysfunction. In order to minimize the long-term impact of obstetrical anal sphincter injuries, women may be referred to a dedicated perineal clinic for early multidisciplinary intervention. Attendance remains an issue at our perineal clinic with 37 % of women choosing not to attend.

The objective of this study was to investigate the clinical factors associated with attendance at a multidisciplinary perineal clinic among patients with an obstetrical anal sphincter injury.

Methods

Our study was a retrospective chart review. All patients who were referred to the multidisciplinary perineal clinic at our tertiary care hospital, with an obstetrical anal sphincter injury, between October 2011 and November 2014, were included in the study. Patients were excluded if they were currently pregnant, suffered a
2nd degree tear or had significant missing data from their charts.

Data management and analysis was carried out using SPSS analytical software. Analyses compared the presence or absence of independent variables between women who attended and did not attend the clinic (the outcome variable). Statistical testing was done using chi-squared test (for 2x2 tables), and t-test for normally distributed continuous variables or Mann-Whitney test for non-parametric variables. This study had a 80% power to detect a between-group difference of 12% for categorical variables (α= 0.05).

Results

245 patients with an obstetrical anal sphincter injury were referred to the clinic. 24 patients were excluded. Analysis was performed on 221 patients of whom 82 did not attend the clinic. Patient age and use of epidural were found to be statistically different between the two groups. The non-attendees were younger and more likely to have had an epidural during labor.

Conclusion

Our research showed that there were few clinical factors associated with the perineal clinic attendance. With further research, we intend to explore socio- economic factors such as childcare, cultural background, transportation and education as those variables are likely to influence attendance. Information from this study will guide changes to facilitate greater attendance at the multidisciplinary perineal clinic and help guide others who are interested in developing a similar clinic.

Funded By:

CORRECTED January 26, 2016

Abstract #: 133
Presenter: Tasneem Siyam
Supervisor: Nese Yuksel
Title: Determinants of Hormone therapy Uptake and Decision Making in Surgically Menopausal Women
Authors: Tasneem Siyam, Jenny Carbon, Nese Yuksel
Affiliations: Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta
Research Activity: Women's Health : Mature Women's Health
Investigation Type: Quantitative Research

Introduction:

Earlysurgical menopause (≤45 years) is associated with significant short and long-term health consequences. The abrupt decline in hormones can lead to severe menopausal symptoms including vasomotor symptoms, sleep disturbances, mood, sexual dysfunction and urogenital symptoms. These patients are also at risk for cardiovascular disease, stroke, cognitive impairment, and osteoporosis. Hormone therapy (HT) is a recommended option in women with no contraindications to HT. However, HT is greatly underutilized among these women due to fear of associated safety concerns. The objective of this study is to identify and describe determinants of HT uptake and decision making in women with early surgical menopause, in scientific literature.

Methods:

We searched Medline, EMBASE and CINAHL, from inception to February of 2015, to identify relevant literature. Search terms used in our search execution were derived from 3 main concepts, surgical menopause, hormone therapy, and decision-making. Words were searched either as subject headings or keywords.
Limitations applied to our search were to English language, and human studies. Our inclusion criteria included studies that assessed factors affecting the uptake and decision making about HT in surgically menopausal women. Studies that included both natural and surgical menopausal women were eligible for inclusion.

Results:

Our search yielded 1,952 articles. Of these 17 fit our inclusion criteria and were included in the review.Socioeconomic status, lifestyle behaviors, medical history and relief of menopausal symptoms were established determinants of HT uptake in both natural and surgical menopausal women. Factors associated with HT decision making in surgically menopausal women included: (1) beliefs on HT benefits; (2) fear of HT associated risks and side effects; (3) influence of information sources (e.g. physicians, media, friends and family); (4) attitudes towards menopause (e.g. medicalized or natural); and (5) use of experiential reasoning to negotiate risks

Conclusion:

Our review identified a number of modifiable determinants of HT decision making that tailored interventions, such as up-to-date, evidence based decision aids, can target to help women with surgical menopause make informed decisions about HT.

Funded By:

women & children's health research institute

Abstract #: 134
Presenter: Humirah Sultani
Supervisor: Nese Yuksel
Title: Evaluating the Content & Development of Decision Aid Tools for the Management of Menopausal Symptoms: A Scoping Review
Authors: Humirah Sultani, Tasneem Siyam, Nese Yuksel
Affiliations: University of Alberta
Research Activity: Women's Health : Mature Women's Health
Investigation Type: Qualitative Research

Introduction: Decision-making during menopause can be complex given the variability in women's risk-benefit perceptions of menopausal treatment options, including hormone therapy. Several decision aid tools (DATs) have been developed to assist women and health care professionals make choices regarding treatment options during natural menopause; however, few have been developed specifically for surgical menopause. The objective of this scoping review is to identify and evaluate the content and development of DATs for menopausal symptoms in natural or surgical menopause.

Methods: This scoping review includes a systematic search of electronic databases from inception to date, including MEDLINE, EMBASE, CINHAL and others, conducted with librarian assistance. All published and unpublished efforts reporting the development of DATs for menopausal symptoms management associated with natural or surgical menopause are eligible for inclusion. Search terms will be derived from two main concepts: menopause and DATs, and will be searched as headings or keywords. The search will be limited to English language and human studies. For identifying additional studies, other searches will be conducted, such as hand searching reference lists of review papers for relevant articles, a Google® web search, as well as a grey literature search that will be completed. Two reviewers will independently screen study titles and abstracts for eligibility. Data extracted by two separate reviewers will include manuscript characteristics, details of target populations, and DAT-specific characteristics pertaining to content and development. This data will be synthesized into evidence tables and narrative summaries. A qualitative integration of findings related to characteristics of the DAT and its quality evaluation by content area, and timing of development relative to women's health initiative (WHI) and the international patient decision aid standards (IPDAS) publications will be included.

Results: The literature search is currently in progress and will be followed by screening, data extraction and data synthesis. We anticipate having scoping review results in time for the WCHRI research day.

Conclusions: This scoping review will help us identify and evaluate existing evidence regarding DATs used for managing menopausal symptoms. This information will help to guide the development of a patient-specific DAT with direct applicability in surgical menopause, with the hopes of helping women make value-based decisions regarding their treatment options.

Funded By:

Abstract #: 135
Presenter: Sabina Baghirova
Supervisor: Richard Schulz
Title: Nuclear matrix metalloproteinase-2 and investigation of its potential functions in ischemic-reperfused hearts
Authors: Sabina Baghirova, Marcia Kondo, Bryan Hughes, Richard Schulz
Affiliations: University of Alberta
Research Activity: Cardiovascular disease
Investigation Type: Quantitative Research

Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent proteases which are known to be involved in extracellular matrix remodeling associated with developmental processes and disease progression. The Schulz lab was the first to report intranuclear MMP activity with MMP-2. MMP-2 has a C-terminal nuclear localization sequence that is exposed on its surface. We hypothesized that MMP-2 is present in the nucleus under normal physiological conditions but increases during oxidative stress induced myocardial ischemia-reperfusion (I/R) injury, proteolyzing structural and DNA repair proteins. Lamin A/C, a putative nuclear MMP-2 target, is an intermediate filament protein that provides structural support to the nucleus. We hypothesized that nuclear lamins might be proteolyzed by MMP-2 during I/R injury.

Methods

Immunofluorescent confocal microscopy was used to visualize the distribution of MMP-2 in neonatal rat ventricular myocytes. Nuclear proteins were isolated from myocytes to test for MMP-2 presence. Rat hearts were isolated and perfused by the Langendorff method aerobically, or subjected to global, no-flow ischemia followed by aerobic reperfusion in the presence or absence of an MMP inhibitor (O-phenanthroline 100μM). Nuclear fractions extracted from the rat hearts were tested for MMP-2 activity and levels. To identify possible target, troponin I, a known sarcomeric target of MMP-2, and lamin A levels were measured by western blotting. An in vitro proteolysis assay was performed by incubating purified lamin A or B with MMP-2 for 2 hours at 37°C.

Results

72kDa MMP-2 activity and protein were present in highly purified nuclear fractions from neonatal myocytes. MMP-2 showed a cytosolic and nuclear staining pattern in myocytes. MMP-2 activity, but not protein level, was increased in nuclear fractions from rat hearts subjected to I/R injury. Lamin A, but not lamin B, was proteolysed by MMP-2 in to a putative 50kDa fragment in vitro, which was also predicted by in silico cleavage site analysis. Troponin I levels in whole heart extracts were decreased in I/R hearts and normalized with O-phenanthroline, however, lamin A and lamin C levels remained unchanged.

Conclusions

Nuclear MMP-2 is present in cardiomyocytes under normal physiological conditions, and is increased as a result of I/R injury. This increase of MMP-2 activity in extracts from I/R hearts leads to proteolysis of troponin I, but not lamin A or C. The activation of genes in myocardial stunning injury suggests that other nuclear functions of MMP-2 are likely.

Funded By:

women & children's health research institute

Abstract #: 136
Presenter: Brandon Chan
Supervisor: Richard Schulz
Title: Potential targets and consequences of myocardial matrix metalloproteinase-2 activation in doxorubicin cardiotoxicity
Authors: Brandon Chan, Andrej Roczkowsky, Bryan Hughes, Richard Schulz
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction:

Doxorubicin (DXR) is an effective antineoplastic agent commonly prescribed in many chemotherapeutic regimens for women's and pediatric cancers. However, DXR chemotherapy causes cumulative, dose-dependent cardiotoxicity, leading to heart failure. Some pre-clinical studies have shown that females are more susceptible to DXR-related heart failure than males. Chronic treatment stimulates oxidative stress and increases matrix metalloproteinase-2 (MMP-2) levels in the heart. MMP-2 is an extra- and intra-cellular protease that plays an important role in heart diseases associated with increased oxidative stress. Intracellular MMP-2 proteolyzes several important proteins, including α-actinin, titin, and troponin I, which regulate cardiac contractile function. Intracellular MMP-2 may play a causative role in DXR cardiotoxicity by cleaving specific proteins in cardiomyocytes.

Hypothesis:

DXR activates intracellular MMP-2 by oxidative stress in cardiomyocytes at an antitumor dose.

Methods:

Human fibrosarcoma (HT1080) cells and neonatal rat ventricular myocytes (NRVM) were treated with DXR (0.5 μM) ± selective MMP-2 inhibitors ARP-100 (1 μM) or ONO-4817 (1 μM) for 2-24 hr at 37°C. MMP-2 activity from cell lysates were measured by gelatin zymography. Levels of MMP-2 and its substrates were measured by immunoblotting. Oxidative stress was assessed by changes in mitochondrial aconitase activity. Cell death was quantified by lactate dehydrogenase release.

Results:

After 24 hr, DXR caused 15% cell death in HT1080 cells but none in NRVM ($n=4$, $p<0.05$). In NRVM, DXR activated intracellular MMP-2 after 12 hr by 310% relative to vehicle control ($n=5$, $p<0.05$). ARP-100 or ONO-4817 attenuated DXR-induced MMP-2 activation by 60% after 24 hr ($n=7$, $p<0.05$). Intracellular MMP-2 activation is caused, in part, by a two-fold increase in MMP-2 protein levels relative to vehicle control ($n=4$, $p<0.05$). At 12 hr when MMP-2 activity was increased, there was a trend of reduced aconitase activity in DXR-treated NRVM ($n=4$). No differences in α-actinin, GSK-3b, SERCA2, and troponin I levels were observed after 24 hr.

Conclusions:

Treatment with DXR at an antitumor dose acutely activates myocardial MMP-2 apparently also by an increase in its protein level. In order to understand how MMP-2 is activated, I will measure oxidative stress at earlier time points. Other MMP-2 targets such as titin are currently being studied. Future experiments in mice will study the sexual dimorphism of DXR in relation to cardiac function, MMP-2 activity, and MMP-2 substrates. These experiments will help determine whether blocking intracellular MMP-2 activity may be a possible adjuvant therapy to prevent DXR-triggered myocardial injury in women and children receiving cancer chemotherapy.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 137
Presenter: Arata Fukushima
Supervisor: Gary Lopaschuk
Title: Acetylation Control Contributes to Maturational Alterations in Energy Metabolism in the Newborn Heart
Authors: Arata Fukushima, Osama Abo Alrob, Liyan Zhang, Cory S. Wagg, Tariq Altamimi, Sonia Rawat, Paul F. Kantor, Ivan M. Rebeyka, Gary D. Lopaschuk
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction: Dramatic maturational changes in cardiac energy metabolism occur in the newborn period, with a shift from glycolysis to fatty acid oxidation. Lysine acetylation has been recently identified as a novel post-translational modification involved in cardiac energy metabolism. We investigated the impact of changes in protein acetylation on the maturational changes in energy metabolism of the newborn rabbit heart. ***Methods and Results:*** One, 7, and 21-day old rabbit hearts were perfused. Cardiac fatty acid β-oxidation rates was increased in 21-day vs. 1-, and 7-day old hearts (555±26 vs. 299±10 and 364±24 $nmol.g\ dry\ wt^{-1}.min^{-1}$), whereas glycolysis and glucose oxidation rates decreased in 21-day old hearts. Increased myocardial acetylation was observed with maturation and associated with increased expression of the mitochondrial acetyltransferase, GCN5L1, while the mitochondrial deacetylase, SIRT3, did not change. Fatty acid oxidation enzymes, long chain acyl CoA dehydrogenase (LCAD) and β-hydroxyacyl CoA dehydrogenase, were hyperacetylated with maturation, positively correlated with their activities and fatty acid β-oxidation rates (R^2 =0.53 and 0.69, respectively). Acetylated PGC-1α is decreased with maturation and involved in increased ATP production, accompanied by increased expression of the nuclear deacetylase SIRT1 in early phase and decreased SIRT6 in late phase. Hypoxia inducible factor 1α expression declined post-birth, whereas acetylation of hexokinase and phosphoglycerate mutase increased. Pyruvate dehydrogenase (PDH) was phosphorylated in 21-day old hearts, whereas acetylated PDH was not changed. ***Conclusions:*** Increased lysine acetylation enhances fatty acid β-oxidation and impairs glycolysis, suggesting a crucial role in maturational change of cardiac energy metabolism in the newborn period.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 138
Presenter: Dora Gyenes
Supervisor: Lisa Hornberger
Title: Altered blood flow in utero and its relationship with neonatal clinical & neurodevelopmental outcomes in children with Hypoplastic Left Heart Syndrome
Authors: Dora Gyenes, Joseph Atallah, Charlene Robertson, Gwen Alton, Winnie Savard, Lisa Hornberger
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Children with hypoplastic left heart syndrome (HLHS), who must undergo three operative stages in the first years of life, are at increased risk of compromised clinical and neurodevelopmental (ND) outcomes. Fetuses with HLHS frequently have altered middle cerebral artery (MCA) blood flow in utero, specifically a low pulsatility index (PI). This physiological phenomenon, typically seen in placental insufficiency, represents decreased cerebral vascular resistance and optimized blood flow to the brain to compensate, so-called "brain sparing". Pregnancies with fetal HLHS have also been found to have a high incidence of placental pathology with likely onset in the 3rd trimester. A high UA-PI is associated with placental insufficiency. In the present study, we investigate the relationship of altered MCA and umbilical arterial (UA) flow patterns in fetal HLHS to neonatal clinical and 2-year ND outcomes.

Methods: We identified all children with HLHS prospectively followed in the Western Canadian Complex Pediatric Therapies Follow-Up Program who had a fetal echocardiogram in the University of Alberta Fetal & Neonatal Cardiology Program between March 2005 and June 2013. Those that died prior to 2 years were excluded. Fetal echocardiograms in the third trimester were analyzed offline, measuring MCA and UA-PI. Clinical neonatal and perioperative parameters were assessed around the initial neonatal operation. Bayley Scales of Infant and Toddler Development-III (cognitive, language, and motor) ND at 2 years were reviewed. Statistical analysis was done using Pearson correlation coefficients.

Results: Thirty-five children met inclusion criteria. Average gestational age at fetal echocardiogram was 39.2 ± 1.4 weeks. Although no neonatal-perioperative parameter correlated with MCA-PI, UA-PI inversely correlated with birth weight ($r = -0.400$, $p=0.019$), and head circumference at birth ($r=-0.478$, $p=0.004$) and at 18-24 months ($r=-0.493$, $p=0.003$), and positively correlated with worse preoperative lactate ($r=0.408$, $p=0.017$), postoperative length of ventilation ($r=0.380$,$p=0.026$) and hospital stay ($r=0.471$, $p=0.005$). With respect to ND outcomes at 2 years, UA-PI and MCA-PI inversely correlated with cognitive outcomes ($r=-0.378$, $p=0.028$ and $r=-0.327$, $p=0.055$, respectively).

Conclusions: Higher UA PI in fetal HLHS was associated with worse clinical perioperative status around the Norwood procedure and 2-year cognitive ND outcomes. This feature of placental insufficiency may be an added mechanism of insult previously unrecognized in HLHS. A lower MCA-PI tended to inversely correlate with higher 2-year ND cognitive scores. This brain-sparing phenomenon may occur in HLHS due to associated placental pathology or the abnormal circulation, and may be protective in the fetus with HLHS.

Funded By: Summer Studentship

Abstract #: 139
Presenter: Sunjidatul Islam
Supervisor: Andrew Mackie
Title: Congenital Heart Disease Hospitalizations in Canada: A 10-year Experience
Authors: Sunjdiatul Islam, Yutaka Yasui, Padma Kaul, Andrew Mackie
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction: The impact of the growing population of children and adults with congenital heart disease (CHD) on inpatient services in Canada is not known. We sought to assess temporal changes in hospitalizations of CHD patients.

Methods: We identified all patients with a CHD diagnosis receiving inpatient care in Canada between fiscal years 2003 to 2012 using the Discharge Abstract Database of the Canadian Institute for Health Information. Poisson regression was performed to assess temporal changes in the annual hospitalization rate.
Hospitalization rates were indexed to both the general population and the estimated CHD population. The numbers and rates of annual hospitalizations were also analyzed stratifying by age group, sex and severity of CHD. A multivariable logistic regression with generalized estimating equation model was used to identify factors independently associated with hospital length of stay>14 days.

Results: A total of 103,034 hospitalizations occurred in 61,051 patients from fiscal years 2003 to 2012. The absolute number of hospitalizations increased by 4.0% per year in adults and 1.3% per year in children. The greatest increase was in patients aged 65+ followed by those 40-64 years.

However, the hospitalization rate in adults varied between 39- 55 per 1,000 CHD population with a reduction of 4%/year (95% CI 0.95 to 0.96, p<0.001). The hospitalization rate in children ranged from 79- 87 per 1,000 CHD population and did not change significantly over time (Rate ratio 1.00, 95% CI 1.00 to 1.01, p=0.035). Males accounted for 53.5% of hospitalizations. Although the proportion of patients with complex CHD was less than those with simple or moderate CHD, there were disproportionately more admissions among complex CHD patients. In adults, late cardiac events such as congestive heart failure, ischemic heart disease, atrial fibrillation and atrial flutter were the most common reasons for hospitalizations. Risk factors for LOS greater than 14 days were age < 1 year, male sex, complex CHD, and having both cardiac surgery and catheterization during the same hospitalization.

Conclusions: The absolute number of hospitalizations with CHD increased over time in both children and adults. However, the hospitalization rate relative to the CHD population decreased among adults, possibly reflecting improved outpatient management. The absolute increase in CHD hospitalizations will pose a financial burden on health care systems.

Funded By:

women & children's health research institute

Abstract #: 140
Presenter: Rachel Joffe
Supervisor: Gonzalo Garcia Guerra
Title: The reliability of invasive and noninvasive blood pressure measurements in unstable critically ill children
Authors: Ari Joffe
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: The accuracy of arterial line blood pressure (BP), and the difference between blood pressure measured by arterial line (AL) versus noninvasive-cuff (NIC) has not been determined in critically ill children.

Methods: After consent, we performed the flush test and stopcock test on indwelling ALs; the primary outcome was describing the incidence of optimally- damped ALs with 95% confidence intervals. The AL-NIC difference between SBP, DBP, and MBP was also determined.

Results: 70 paired comparisons were determined, in patients age 41.4 (SD 49.8) [IQR 5-75] months, male 36 (52%), post-operative cardiovascular surgery 43
(61%), medical-surgical 27 (39%), on inotropes 24 (34%), vasodilators 12 (17%), and ventilation 61 (87%). Few had factors that impact NIC-BP reliability: obesity 7
(12%), severe arm edema 3 (4%). ALs were in for 1-3 days in 42 (60%), 4-6 days 19 (27%), and 7-10 days 3 (13%); 55 (79%) had peripheral and 15 (21%) central
(femoral) ALs. The flush test performed in 29 (42%) patients found the AL optimally damped in 13 (45%) [95% CI 28 to 62%], overdamped in 16 (55%), and
underdamped in 0 (0%). The stopcock test in 70 patients found the AL optimally damped in 6 (9%) [95% CI 4 to 18%], overdamped in 62 (90%), and underdamped in 1 (1%). The result of the flush test and stopcock test were the same in 17/28 (61%) [95% CI 42 to 76%] of patients. Some (n=15 flush, and n=30 stopcock) patients had a second set of tests 2 hours later, and the results were similar. The correlation for SBP, DPB, and MBP between AL and NIC was excellent (r=0.89, 0.79, 0.86 respectively). However, the difference between SBP, DPB, and MBP (AL-BP minus NIC-BP) ranged widely, with large Standard Deviation (SD), Inter-Quartile Range (IQR), and range. The difference between SBP was mean 1.3 (SD 11.3), median 3.5 [IQR -4.3, 9], range 53; DBP mean 0.6 (SD 12.3), median
1.5 [IQR -6, 7], range 79; and MBP mean 3.3 (SD 9.8), median 4 [IQR -1, 9], range 57. Results of the second comparison were similar.

Conclusions: Only half of ALs in PICU are optimally damped (accurate), with the rest overdamped, potentially underestimating BP. The stopcock test was not reliable, with results differing from the gold-standard flush test in 39%. Although NIC and AL BP correlated well, the difference between SBP, DBP, and MBP ranged widely, suggesting that NIC-BP is not reliable in critically ill children.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 141
Presenter: Deliwe Ngwezi
Supervisor: Lisa Hornberger
Title: Industrial Developmental Toxicant Emissions and Congenital Heart Disease in Urban and Rural Alberta, Canada
Authors: Deliwe Ngwezi, Jesus Serrano-Lomelin, Deborah Fruitman, Alvaro Osornio-Vargas
Affiliations: University of Alberta
Research Activity:
Investigation Type:

Introduction: Our previous results based on risk scores (toxicity) of the developmental toxicants (DTs), suggested a spatio-temporal association between mixtures of organic compounds released from industrial sources and congenital heart disease (CHD) in Alberta. In the current study we hypothesized that the downward temporal associations between developmental toxicants (DTs) and CHD would have a different industrial sector participation in the urban and rural areas of Alberta.

Methods: Data sources: 1) Extracted DTs released to air from industrial sectors in Alberta as reported in Canada's National Pollutant Release Inventory from 2003-2010 2) CHD cases born between 01/01/04-31/08/11 from Stollery and Calgary Childrens' Hospitals Xcelera databases 3) Annual births are reported at provincial level, therefore census 2011 was used to assign modeled infant birth denominator for urban and rural areas using Forward Sortation Areas in order to calculate crude CHD rates. Principal Component Analysis was undertaken to reduce the dimensionality of the number of DTs and the solution was applied to rural and urban areas to test correlations with corresponding CHD rates.

Results: We retained 3 principal components (PC): PC1 consisted of mixture of organics and gases, PC2 consisted of mixture of organics only and PC3 consisted of metals. There were strong positive correlations between urban PC1 and rural PC2 with CHD rates, (r= 0.74, p=0.03; r= 0.80, p= 0.02) respectively. In the urban areas, PC1 emissions from mining and manufacturing strongly correlated with CHD (r=0.76, p=0.03; r=0.74, p=0.04, respectively). Finally in the rural areas, PC1 emissions from the mining and utilities positively correlated with CHD rates overall (r=0.71, p=0.05; r=0.74, p=0.04, respectively); whereas, PC2 emissions from mining and manufacturing were positively correlated with CHD (r=0.86, p=0.01; r=0.74, p=0.04, respectively) There were differences in the participation of these sectors for the urban and rural areas.

Conclusions: The current analysis using total amounts of the DTs shows consistency with previous results which used risk scores. Overall the organics are positively correlated with rates of CHD and the difference being the urban CHD rates which are associated with the mixture containing gases. This may point to different industrial activities in urban and rural settings.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 142
Presenter: Mohammad Refaei
Supervisor: Joseph Atallah
Title: Temporal correlation of RSR' pattern on Electrocardiograph to Echocardiographic findings in patients with isolated Secundum Atrial Septal defects
Authors: Mohammad Refaei, Sunjidatul Islam, Joseph Atallah
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Cardiology
Investigation Type: Quantitative Research

Introduction:

Characteristic ECG changes, specifically an rSR' pattern in lead V1, have been described in association with ASDs and left-to-right shunt. We aimed to determine if specific temporal ECG changes can guide a more discriminate and cost-effective echocardiographic screening approach during routine follow-up of isolated secundum ASDs with undetermined hemodynamic significance.

Methods:

Our study population included all pediatric patients followed at the Stollery Children's Hospital with a secundum type ASD, not associated with other significant congenital heart disease. We collected information regarding their ASD size as well as ECG parameters on first and last clinical evaluation.

Results:

We identified 141 patients with ASD. An rSR' pattern on initial ECG was present in 35 (24.8%) patients, 27 of whom had a moderate-to-large ASD (>5mm). of 37 patients underwent operative intervention for their ASD, 19 of whom had rsR' pattern on initial ECG, and 13 of these had maintained the same pattern on pre- operative ECG. Patients with non-rSR' patterns were most likely to be present in those who had their ASD either spontaneously closed or remained the same (across all ASD sizes).

Conclusions:

Our study reports lower prevalence of rsR' pattern in pediatric patient population with ASD, including those with moderate-to-large size ASD. This pattern did not correlate with significant hemodynamic changes or operative outcome. Therefore, rSR' pattern on ECG is not a reliable tool to screen or follow-up patients with hemodynamically stable, isolated secundum ASD.

Funded By:

women & children's health research institute

Abstract #: 143
Presenter: Pranidhi Baddam
Supervisor: Daniel Graf
Title: Identification of phenotypic abnormalities in mice with a neural crest-specific deletion of BMP7 using microCT and morphometric analysis.
Authors: Pranidhi Baddam, Wei Liu, Christopher Parcival, Zeba Malik, Benedikt Hallgrimsson, Daniel Graf
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Quantitative Research

Introduction: Craniofacial tissues are affected in three out of four human congenital birth defects. Knowledge of the genetic basis for such malformations is critical to understand their aetiology and offer optimal patient treatment. Modeling human genetic disorders in the mouse has proven extremely powerful for untangling the molecular and cellular interactions that direct and coordinate craniofacial development.
Bone morphogenetic proteins (BMPs) are signalling molecules involved in most, if not all, developmental processes. BMP7, a crucial osteogenic signalling molecule, in particular regulates the development of various oral and facial structures. Complete loss of Bmp7 leads to a cleft palate and perinatal death precluding analysis of its effects on postnatal craniofacial growth. Cranial neural crest cells form a critical component of the craniofacial structures. Here we report on the deletion of *Bmp7* in neural crest cells (Bmp7fl:wnt1Cre). We identify various craniofacial abnormalities, which using quantitative morphometric analysis can be correlated to facial growth.

Methods: We analysed micro-Computertomography (µCT) datasets using Amira software and landmarks were placed using geometric locations and Cartesian coordinates of the mice heads from 4 day, 8 day, 3 week, 1.75month, 2.75month and 4 month-old mice.

Results: The morphometric analysis of the BMP7 mutant mice revealed several phenotypic abnormalities including shorter mandible, depressed maxilla outgrowth, delayed mineralization of incisors, submucosal cleft palate, and mild to severe blockage of the airways. In several age groups, mice also expressed ossification phenotypes, such as an incomplete closure of the fontanella, and reduced ossification of the frontal and sagittal sutures. Noteworthy, mice with a strong reduction in ossification also presented with dome-shaped heads, in part the result of a premature fusion of sutures along the nasal bones.

Conclusions: This work establishes a critical role of neural crest-derived Bmp7 for the development of craniofacial structures. Lack of BMP7 leads to malfunctioning of several of such structures; detailed analysis of which will enable identification of affected underlying cellular and molecular interactions. The multiple phenotypic consequences caused by the lack of BMP7 provide an excellent model to better understand neural crest-derived congenital complications as well as improve preventable and ongoing treatments.

Funded By: Canada Summer Jobs

Abstract #: 144
Presenter: Vanessa Carias
Supervisor: Rachel Wevrick
Title: The role of MAGEL2, a protein implicated in Prader-Willi syndrome, in the regulation of E3 ubiquitin ligases
Authors: Vanessa Carias, Rachel Wevrick
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder of the nervous and endocrine systems characterized by developmental disabilities, obesity, excessive daytime sleepiness and night-time wakening, and autism spectrum disorder. One of the genes implicated in PWS is MAGEL2. The exact cellular role of MAGEL2 remains to be elucidated. MAGE proteins interact with RING-zinc finger-type E3 ubiquitin ligases and enhance their activity. E3 ubiquitin ligases participate in protein ubiquitylation, a cellular process in which substrate proteins are recognized, ubiquitylated, and targeted for proteosomal degradation. Protein ubiquitylation is implicated in the regulation of diverse processes including cell cycle, intracellular signaling, and transcription. TRIM32 is an E3 ligase that may interact with MAGEL2 and has been implicated in other disorders such as Bardet-Biedl intellectual disability/obesity syndrome and Limb-girdle muscular dystrophy type 2H.

Methods

To determine if MAGEL2 has an effect on E3 ligase TRIM32 abundance and its mutants they will be co-transfected in U2OS cells and analysed by western blotting. Co-localization of these proteins will be determined using immunofluorescence, as well as determining if TRIM32 mutants change this co-localization. A co-immunoprecipitation experiment will be performed to determine if these proteins directly interact. Finally, we will determine if MAGEL2 has an effect on the regulation TRIM32 and its substrate ubiquitination levels.

Results

MAGEL2 has an effect on E3 ligase TRIM32 abundance in U2OS cells. There is more TRIM32 when it is co-transfected with MAGEL2. MAGEL2 also has an effect on TRIM32 mutant constructs, different from the effect on wild-type MAGEL2. MAGEL2 co-localizes with TRIM32 and some of the TRIM32 mutants in the perinuclear region.

Conclusion

The results from this project will elucidate the role of protein ubiquitination in cellular processes that can contribute to PWS symptoms. We will further understand how loss of MAGEL2 in children with complex autism/obesity and children with PWS causes the various findings associated with these complex disorders.

Funded By: Graduate Studentship

Abstract #: 145
Presenter: Christelle Dzolang
Supervisor: Oana Caluseriu
Title: A novel, rare SF3B4 missense mutation, as a possible cause for Nager syndrome
Authors: Christelle Dzolang, JS Bamforth, K Atta, Erin Garside, Andrew MacMillan, Oana Caluseriu
Affiliations: University of Alberta
Research Activity: Limb abnormalities, congenital deformation
Investigation Type: Quantitative Research

A novel, rare SF3B4 missense mutation, as a possible cause for Nager

syndrome. **Introduction:**

Nager syndrome (NS; OMIM 154400) is the prototype for a group of disorders called acrofacial dysostoses characterized by mandibulofacial and limb anomalies. NS is an autosomal dominant genetic disorder with a variable, multisystemic involvement but hallmarks of the condition are a recognizable facial gestalt including downslanted palpebral fissures, malar hypoplasia, and micrognathia, and most commonly preaxial, predominantly upper limb anomalies including aplasia/hypoplasia of the thumb and radioulnar synotosis. In 2012, Bernier et al, have hypothesized that haploinsufficiency of SF3B4 is the cause of 61% of the individuals clinically diagnosed with NS in their cohort. Published pathogenic mutations associated with NS include a specific missense in the initiator Met, nonsense, frameshift, and splicing mutations. To our knowledge, no other pathogenic NS missense mutations have been published to date. SF3B4 encodes SAP49, a highly conserved spliceosomal protein, with two RNA recognition motifs (RRMs) followed by a proline-glycine rich domain. During assembly of the U2SNP prespliceosomal complex, SAP49 binds to the pre-mRNA just upstream of the branch point sequence and is believed to play a crucial role in tethering the U2 snRNP to the branch site.

Methods:

Our patient, a 12years old boy, presented with downslated palpebral fissures, zygomatic hypoplasia, micrognathia, bilateral hypoplastic thumbs, conductive hearing loss, and speech delay consistent with a likely diagnosis of Nager syndrome. Direct sequencing of the entire coding region of SF3B4 was undertaken by standard PCR and Sanger methods. Mutational *in silico* analysis was done through SIFT, Mutation Taster, Polyphen, and Pymol.

Results:

A novel variant (c.251T>G) in exon 3 of SF3B4 was identified that replaces an isoleucine (hydrophobic amino acid) by an arginine (basic amino acid). *In silico* analysis (SIFT, Mutation Taster, Polyphen) indicate that this change is deleterious/ disease-causing. This mutation is situated in the first RRM of SF3B4, and protein homology and conformation study (Pymol) indicate severe disruption of SAP49 at an essential site. Mutation was confirmed to be *de novo* in the patient. Further functional studies are under way to confirm pathogenicity.

Conclusion:

We are reporting the first patient with a clinical diagnosis of NS and a rare SF3B4 missense mutation outside the initiator Met, likely pathogenic. This finding expands the repertoire of genetic mutations in NS and opens the possibility of exploring and understanding in more details the complex splicing machinery involved in a growing group of genetic disorders called spliceosomopathies.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 146
Presenter: Sara Laughton
Supervisor: Deryk Beal
Title: A family history study of developmental stuttering: Preliminary analysis.
Authors: Grace Lee , Sara Laughton , Tara Dzwiniel, Deryk Beal
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Mixed Methods

Introduction: Developmental stuttering is a communication disorder characterized by involuntary repetitions, prolongations of speech sounds or silent blocks impairing speech production. The disorder has its onset in early childhood (typically ages 2-5 years), and affects 5-8% of children with a higher prevalence in boys. This study is part of the larger project: Genetic Contributions to Developmental Stuttering, which explores the genetic underpinnings of this disorder through incidence and aggregation analyses, and DNA sequencing.Here we report the project's progress to date; data collection is complete, DNA samples are banked, and analysis is ongoing. Preliminary incidence data and developmental milestone data for our child cohort as compared to developmental norms are presented.

Methodology: Through a self-report questionnaire, 165 probands who stutter (age 6-85, mean age 29.55) reported developmental and medical histories, and provided a three generation family history. All known family members affected with stuttering and/or a speech, language, or learning disorder were noted. Parents of child probands reported on their behalf. As developmental stuttering has its onset in the preschool years, this preliminary report focusses on our child cohort of 55 children and adolescents (age 6 - 17, mean age 11.58, 46 M: 9 F).

Results: The average age of stuttering onset in our child cohort was 48 months.The mean reported for age of first word production was 15 months for boys and 12 months for girls. Two-word combinations were first produced at an average age of 22 and 21 months for boys and girls respectively, and both genders first used sentences on average at 28 months. Initial analyses of all probands revealed 65.7% had a positive family history of stuttering and 13.3% of first order relatives (i.e. parents and siblings) were also affected by developmental stuttering.

Conclusions: Overall our children who stutter demonstrated normal developmental milestones for language production. Previous research has reported that 30- 60% of people who stutter and less than 10% of people who do not stutter had a positive family history of stuttering. Past studies have reported 16-17% of first order relatives affected with developmental stuttering, which is higher than our study. However, our data adds to this body of research demonstrating a genetic link in transmission. As analyses continue for this massive database we aim to determine how stuttering aggregates in families and which familial relations are at highest genetic risk. Our DNA collection will help guide future genetic and molecular studies to further understand this complex disorder.

Funded By: Innovation Grant

Abstract #: 147
Presenter: Sonya Widen
Supervisor: Andrew Waskiewicz
Title: Identification of a novel cause of ocular coloboma
Authors: Sonya Widen, Prajakta Desai, Mika Asai-Coakwell, Matthew Benson, Ordan Lehmann, Andrew Waskiewicz
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Congenital Abnormalities
Investigation Type: Quantitative Research

Introduction

Microphthalmia (small eyes), anophthalmia (no eyes) and coloboma are a group of related, frequently blinding conditions that result from abnormal embryonic eye development. Collectively referred to as MAC, these defects represent up to 11% of all pediatric blindness. Our lab and others have previously implicated bone morphogenetic protein (BMP) signaling, a crucial developmental signaling pathway, in causality of MAC. However, our understanding of direct causes of MAC only represents a fraction of documented cases. Our goal is to elucidate the genetic causes of these pediatric diseases. Here, we describe our latest work on an intriguing new candidate, *BMP3*.

Methods

To identify the genetic causes of MAC, we performed Sanger and exome sequencing. We employed morpholino (MO)-based gene knockdown to investigate the role of *bmp3* in ocular development, in situ hybridization (ISH) for gene expression analysis and transgenic zebrafish for fluorescent microscopy and cell migration analysis. We utilized luciferase reporter assays, western blots and *in silico* ANOLEA modeling to investigate the pathogenicity of identified mutations.

Results

Exome sequencing of a family of affected individuals identified a sequence variant in *BMP3*, with two additional variants identified within the mature protein domain through Sanger sequencing of a MAC panel. *In silico* modeling indicates these variants are highly damaging to protein structure, while *in vitro* assays suggest BMP3 variants have altered biological activity. To investigate the role of *bmp3* in ocular development, we performed *in vivo* experiments in zebrafish. While ISH revealed that *bmp3* is expressed not in the eye but immediately anterior to it, MO knockdown of Bmp3 causes MAC, lens defects and other ocular abnormalities, highlighting a key role for *bmp3* in eye formation. Additionally, MO knockdown causes ectopic BMP signaling in periocular mesenchyme (POM), an extraocular group of cells that migrates to the optic fissure and has been implicated in causality of MAC. A role for BMP signaling in POM-mediated fissure closure remains unknown. Consistent with lens defects, a POM-derived structure, and the incidence of MAC, MO knockdown of *bmp3* causes defects in POM migration.

Conclusions

We have identified a novel candidate in causality of MAC, *BMP3*. Sequence variants identified in MAC patients are predicted to be damaging to both protein structure and biological activity. Zebrafish experiments suggest loss of Bmp3 causes not only MAC, but incorrect migration of POM cells, suggesting a possible mechanism for the action of Bmp3 in ocular development.

Funded By: Graduate Studentship

Abstract #: 148
Presenter: Tishani Methsala Wijesuriya
Supervisor: Rachel Wevrick
Title: Role of the Prader-Willi Syndrome protein MAGEL2 in leptin receptor function in obesity pathways in the brain.
Authors: T.Methsala Wijesuriya, K.Vanessa Carias, Rachel Wevrick
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Mental Health
Investigation Type: Qualitative Research

Introduction: Loss of function of MAGEL2 may contribute to obesity in children with Prader-Willi Syndrome. Children with Prader-Willi syndrome have neonatal feeding difficulties, developmental delay and excessive appetite. They develop excess fat tissue in childhood, and in the absence of strict intervention, they typically develop life-threatening obesity. MAGEL2 is important in the brain cells that sense how much fat the body has by measuring how much leptin is in the bloodstream. Leptin is a hormone that acts on hypothalamic neurons to regulate the appetite. MAGEL2 protein is important for recycling or degradation proteins in the brain by interacting and modifying the activity of E3 ubiquitin ligases. The RNF41 protein is a E3 ubiquitin ligase associates with a ubiquitin- specific protease (USP8). Together with USP8, RNF41 regulates the recycling of the leptin receptor by targeting it either for degradation of for recycling to the cell membrane. We hypothesized that MAGEL2 normally regulates the interaction between RNF41 and USP8, and that loss of this regulation could impair leptin response pathways in the brain in children with PWS.

Methods: Human U2OS cells were transfected with recombinant constructs encoding epitope tagged versions of MAGEL2 and RNF41 wild type and mutant forms RNF-SQ and RNF-AE. Protein lysates were collected after 48 hours. Co-immunoprecipitation assays were done by antibodies against FLAG, HA and RNF41. Immunofluorescence was done to visualize the co-localization of different forms of RNF41 with MAGEL2 in intracellular compartments. We expressed recombinant MAGEL2, RNF41 and USP8 in combinations in human U2OS cells and examined the relative abundance of each protein in the presence or absence of the other components of the complex.

Results: Abundance of RNF41 was higher when MAGEL2 was co-expressed, and abundance of MAGEL2 was higher when RNF41 was co-expressed. This suggests that MAGEL2 and RNF41 proteins stabilize each other inside the cell. Abundance of RNF- SQ mutation was higher, while abundance of RNF-AE was lower when MAGEL2 was co-expressed. Preliminary results suggest that MAGEL2 modifies the ability of RNF41 to auto-ubiquitinate or to ubiquitinate MAGEL2.

Conclusion: This study will help to understand how MAGEL2 modifies the activity of the RNF41-USP8 ubiquitination complex, and how it regulates the intracellular sorting, recycling or the degradation of the brain receptors for leptin. This study will elucidate how the loss of MAGEL2 contributes to obesity in children with Prader-Willi syndrome.

Funding: This study was funded by the Canadian Institutes of Health

Research. Funded By: CIHR

women & children's health research institute

Abstract #: 149
Presenter: Abeer Alzaben
Supervisor: Diana Mager
Title: Ethnicity influences quality of life in youth with Celiac Disease on the gluten free diet.
Authors: Leanne Shirton , Rabin Persad , Justine Turner , Diana Mager
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Nutrition
Investigation Type: Quantitative Research

Introduction: Little is known about the quality of life (QoL) in youth of varying ethnicities with Celiac Disease (CD) following a gluten-free diet. The study objectives were to measure QoL in youth with CD of varying ethnicities and to investigate the socio-demographic and anthropometric factors influencing QoL.

Methods: Youth with biopsy proven CD (10±3 years) and following the gluten-free diet for more than 6 months were recruited. Demographic, Anthropometric
and laboratory data was collected. QoL was measured using the parent-proxy and child-reports for PEDSQL 4.0.

Results: A total of 52 youth with CD (15M, 37F) were recruited; 65% (n=34, 10±4 years) were Caucasian (CAU) and 35% (n=18, 11±4 years) were non-Caucasian (n- CAU). No differences were found in age of diagnosis (CAU: 7±4 years; n-CAU: 8±3 years), the duration of CD (CAU: 2±1 years; n-CAU: 3±3 years), and anti- tissue transglutaminase level (ATTG) (CAU: 9±7 IU/mL; n-CAU: 10±11 IU/mL) between the two groups (p>0.05). Adherence to GFD was reported in 87% (n=30) of CAU group and 77% (n=14) of n-CAU (p>0.05). Abdominal pain was reported in 41% (n=14) of CAU group and 44% (n=8) of n-CAU (p>0.05). CAU group had higher weight-for-age z-score (CAU: 0.09±0.93; n-CAU: -1.12±1.57; p=0.003) and height-for-age z-score (CAU: -0.16±0.94; n-CAU:-0.87±1.22; p=0.036) than n- CAU group. CAU group (81±11) reported lower average QoL score than n-CAU group (88±19) (p=0.010). The average of emotional (CAU: 68±20; n-CAU: 85±12; p=0.003), social (CAU: 86 ±14; n-CAU: 94±9; p=0.033) and psychosocial (CAU: 76±14; n-CAU: 86±9; p=0.009) scores was lower in CAU than n-CAU group. The parent of CAU group reported lower scores in emotional (CAU: 62±22; n-CAU: 79± 12; p=0.003), social (CAU: 84±17; n-CAU: 94±11; p=0.021) and psychosocial (CAU: 73±16; n-CAU: 84±11; p=0.009) domains than the parent of n-CAU group. No relationship was found between abdominal pain and QoL domains between CAU and n-CAU (p>0.05).

Conclusions: CAU youth with CD reported lower psychosocial QoL than n-CAU youth with CD. Lower QoL in CAU youth was not related to the age, age at diagnosis, the duration of the disease, abdominal pain, parent's age. More studies need to conduct to explore the factors that decrease QoL in CAU youth with CD.

Funded By: Canadian Foundation for Dietetic Research and Practice and Canadian Celiac Association

women & children's health research institute

Abstract #: 150
Presenter: Ghazal Danesh
Supervisor: Eytan Wine
Title: Enhanced elimination of enteric pathogens by macrophages through NLRP3 activation
Authors: Ghazal Danesh, Michael Bording-Jorgensen, Eytan Wine
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Infection, Inflammation, Immunology
Investigation Type: Quantitative Research

Introduction: Inflammatory bowel diseases (IBDs) are lifetime debilitating intestinal disorders that affect up to 0.5% of the Canadian population. The cause of IBD is unknown, but links to environmental conditions, genetic variants, and microbial factors have been determined. A mutation in the gene for the nod-like receptor protein complex 3 (NLRP3) is associated with an increased susceptibility to Crohn disease, a type of IBD. This protein is part of a family of protein complexes called inflammasomes which recognize many different danger signals to promote the secretion of proinflammatory cytokines, such as interleukin-1β (IL-1β), to fight infection. Genetic variants linked to increased susceptibility in Crohn disease elicit a decrease in the expression of NLRP3, leading to the reduced production of IL-1β. Previous work in the Wine lab has shown that mice lacking the NLRP3 protein are more susceptible to infection with an intestinal pathogen and that the addition of IL-1β reverses this effect. The aim of this project was to assess whether inflammasome activation is required for macrophages to uptake and eliminate bacteria, in mouse and human macrophages.

Methods: Gentamicin protection assays were used to quantify the elimination of nonpathogenic and pathogenic strains of Escherichia coli in mouse macrophage (J774A.1) and human macrophage (THP-1) cell lines, in the presence of inflammasome activators and inhibitors. Bacterial plating and Immunofluorescence were used to quantify intracellular bacterial survival. Western Blot was used to confirm inflammasome activation by ATP.

Results: The number of pathogenic intracellular bacteria decreased in both J774A.1 and THP-1 cells when exposed to ATP, an NLRP3 activator, indicating increased bacterial clearance. This affect was not found in the nonpathogenic strains. Inflammasome inhibitor KCl had an inverse effect. We also confirmed these findings with immunofluorescence. Additionally, we investigated IL-1β secretion by J774A.1 cells, with Western blotting. These mouse macrophages secreted increased levels of IL-1β when exposed to bacteria only or bacteria and ATP, compared to control cells. Exposure to KCl inhibited IL-1β release, even in the presence of ATP.

Conclusion: Our results suggest that NLRP3 activation increases bacterial killing by mouse and human macrophages and may do so through the enhanced production of IL- 1β. Nonpathogenic E. coli was not affected by the addition of ATP, which suggests a role for specific microbial virulence factors in inflammasome activation.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 151
Presenter: Lina Maria Becerra
Supervisor: Kim Adams
Title: Using Robots to access play for children with Severe Disabilities
Authors: Lina Maria Becerra, Kim Adams, Adriana Rios, Maria Fernanda Gomez, Javier Castellanos
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Mixed Methods

Study Design: Experimental crossover trials were conducted with 14 typically developing children.

Purpose: To establish if robot play scenarios elicit play at similar developmental levels as when children directly manipulate toys.

Hypothesis: Frequency of pretend play actions increases with age for both direct manipulation and robot play.

Summary of Background Data: Children with severe physical disabilities can have the same play behaviors as typically developing children, but these behaviors may appear late in their development due to difficulty participating in free play activities. Often adults or peers will manipulate toys and suggest play themes, which reduces opportunities for children to explore their environment and control their own play. For this reason, children with severe physical disabilities need a means for manipulating objects in play in order to reveal and develop pretend play.

Methods: Typically developing children between the ages of 3 and 7, participated in free play activities. Conditions for the activities were randomly selected before each session and consisted of playing with conventional toys or unstructured materials through direct manipulation or with a robot. Modeling of using the robot in pretend play was given when children did not perform pretend play naturally. Each session was videotaped and the frequency of each type of play (no play, functional or pretend) was assessed. Inter-rater reliability was 89%.

Results: We will perform statistical analysis once we reach 6 participants per age group, but visual analysis is showing some trends. More pretend play is presented with conventional toys, for all conditions. When *direct manipulation* and *robot before modeling* are compared, for both conventional and unstructured materials, the frequency of pretend play actions decrease. Also, a larger portion of the sessions were coded as no play for more children. It was also observed that when modeling was provided there was an increase in the frequency of pretend play actions for most children. So far, we are not seeing a trend of higher frequency of pretend play for older children in direct manipulation or robot conditions.

Conclusion: Though there is no trend showing the developmental sequence of functional and pretend play for typically developing children, we do see that the robot play scenarios are eliciting pretend play, especially after modelling. Children appear to not know how to involve the robot in their free play, likely they are performing more functional play while exploring the novel robot.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 152
Presenter: Jeff Bennett
Supervisor: Andrea Haqq
Title: Autism Spectrum Disorder in Children with Prader-Willi Syndrome
Authors: Jeff Bennett, Michelle Mackenzie, Sandy Hodgetts, Andrea Haqq, Lonnie Zwaigenbaum
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

Background: Prader-Willi syndrome (PWS), a rare genetic disorder caused by the lack of expression of paternal genes from chromosome 15q11-13, has been compared to autism spectrum disorder (ASD) in various studies. However, no studies investigating ASD symptomatology in PWS have studied exclusively children.

Methods: Our study investigated symptoms of ASD in ten children with PWS using various assessment tools to measure ASD symptoms and non-ASD related social skills and adaptive functioning. The ADOS-2 is considered a gold standard ASD assessment tool based on excellent sensitivity and specificity when compared to clinical best estimate (CBE) (best practice in ASD diagnosis). We describe the ASD symptomatology, based on results from the various ASD assessments, and compared agreement between the assessments. Furthermore, a developmental pediatrician used CBE to decide whether a diagnosis of ASD was warranted for any of the children.

Results: Each child is described, based on results from the assessments. The sample mean for each ASD assessment found scores close to or slightly above the cut-offs for ASD. Despite having eight of ten children exceed cut-offs on at least one of the ASD assessments, only one child exceeded cut-off on all four assessments; however, none of the children were assigned a diagnosis of ASD based on CBE.

Conclusions: Restricted or repetitive behaviors and interests may be the most common ASD-related impairment in children with PWS, but further studies with larger sample sizes are required to verify this. The lack of agreement between the assessments warrants further research into the validity of ASD assessments in a PWS specific sample.

Funded By: Clinical Research Seed Grant

women & children's health research institute

Abstract #: 153
Presenter: Isabel Light
Supervisor: Carmen Rasmussen
Title: Screening for FASD: The Neurobahvioral Screening Tool and neuropsychological functioning
Authors: Isabel Light, Kathleen O'Connor, Kelly Nash, Gail Andrew, Gideon Koren, Carmen Rasmussen
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Fetal Alcohol Syndrome
Investigation Type: Quantitative Research

Introduction

Fetal Alcohol Spectrum Disorder (FASD) refers to neuropsychological, physical and growth deficits that occur to an individual who was exposed to alcohol in utero. The NST is a caregiver report composed of 10 questions from the Child Behavioral Checklist pertaining to externalizing and impulsive behaviors commonly observed in children with FASD. Previous research has found that the NST has good sensitivity rates and excellent specificity against typically developing children. This research examined whether scores on the NST, administered prior to an FASD assessment, are correlated with neuropsychology test scores conducted as part of the FASD assessment. We hypothesized that children with poor scores on the NST, indicative of more problem behaviors, would have neuropsychological phenotype of children with FASD.

Methods

We utilized data collected as part of a larger prospective study on the NST. Participants included 54 children with PAE, aged 6 to 18, whose caregivers completed the NST *prior* to their child being assessed in the FASD clinic through the Glenrose FASD clinic. We calculated a total NST score by summing the number of items endorsed. Neuropsychological tests included measures of Executive functioning (EF), memory, intelligence, and both caregiver and teacher reports of Behavioral EF.

Results

Of the children with Prenatal Alcohol Exposure (PAE) referred for an FASD assessment, 28 received a diagnosis of FASD and 26 did not. The NST screened 57% of children with FASD as positive and 65% of the children with PAE as positive. Correlation analysis was used to examine correlates between neuropsychological test scores and the NST scores. No measures of executive functioning were related to total NST score. IQ was not related to total score on the NST, however higher Verbal comprehension Index was related to poorer NST scores (p<.01). Interestingly parent endorsements of difficulty in behavioral EF were related to poorer scores on the NST (ps<.01), however teachers ratings of behavioral EF were not.

Conclusions

Total NST scores are not related to objective measures of EF. This suggests that the NST may measure 'Hot EF' rather than 'Cold EF'. The NST was not correlated with hypothesized neuropsychological measures, suggesting that the NST may be more sensitive to the behavioral phenotype of FASD rather than the neuropsychological phenotype.

Funded By: Summer Studentship

women & children's health research institute

Abstract #: 154
Presenter: Antoinette Nguyen
Supervisor: Jerome Yager
Title: Alterations in neuronal development and glial maturation following fetal inflammation in the neonatal brain
Authors: Antoinette Nguyen, Edward Armstrong, Jerome Yager
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

Introduction: *In utero* inflammation can result in fetal inflammation (FI), an inflammatory response in the fetus, and is associated with several neurodevelopmental disorders such as cerebral palsy. Currently, there are no available interventions to prevent cerebral palsy. This has directed our laboratory to investigate the therapeutic properties of the natural health product, broccoli sprouts (BrSp), as a prophylactic intervention against the FI. The objectives of the study was to: 1) characterize changes in brain development by assessing neuronal growth, synaptogenesis, and oligodendroglial maturation induced by FI, 2) determine the response of the supporting glial cells, microglia and astrocytes, to FI and BrSp, and 3) investigate the neuroprotective properties afforded by BrSp.

Methods: Intraperitoneal injections of lipopolysaccharide (LPS, 200 mg/kg) were administered to pregnant Long-Evans rats every 12 hours on gestational day (GD) 19 and 20 to mimic *in utero* inflammation. Dietary supplementation with BrSp (200 mg/day) was given to pregnant dams from GD14 to postnatal day (PD)
21. A total of 4 groups were used in the study: (1) saline, (2) saline + BrSp, (3) LPS, and (4) LPS+ BrSp. Brain tissue from newborn PD1, PD7, and PD21 rat pups was collected for subsequent analyses.

Results: Gap43, a marker of neuronal growth cones, was decreased in the LPS and LPS + BrSp groups on PD1 and PD7 compared to controls, however, this was not significant. Synaptophysin, a marker of synaptic proteins, is increased in the cortex of both LPS and LPS + BrSp groups on PD21, however, this was not significant. The presence of oligodendrocytes, identified by the marker Olig2, was decreased in the LPS group on PD1, but these changes were not significant. No differences in activated microglia activity were observed. There was reduced GFAP, a marker of astrogliosis, in PD1 and PD7 brains of LPS pups. On PD21, GFAP was increased in the cortex in both LPS and LPS + BrSp brains compared to controls. These changes in GFAP levels did not reach significance.

Conclusions: Our objective was to characterize alterations in brain development following in utero inflammation and the neuroprotective properties of BrSp. Our data did not detect any significant differences in the markers studied, however, further investigations are still underway to determine the pathophysiology associated with our model of FI.

Funded By: Start-up or Retention Funding

Abstract #: 155
Presenter: Lexa Peters
Supervisor: Debra Andrews
Title: Developing skills for developmental disabilities – evaluating effectiveness of a new elective
Authors: Lexa Peters, Raisa Kanji, Sarah Riedlinger, Debra Andrews
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Neuro-cognitive Development
Investigation Type: Quantitative Research

Introduction:

Many medical students feel they do not receive sufficient training in physical and cognitive disability (Burge et al., 2008; Jurczyk & Kelly, 2009). This may translate into impaired clinical skills for identification of developmental delays in the pediatric population. Medical students and physicians may require formal training to correctly identify children at risk of developmental delay to arrange for proper referral. Our clinical question was: "Does formal training in developmental disability, presented as a 12 hour preclinical elective, increase preclinical medical students' confidence and ability to interact with children with disabilities and their families?"

Methods:

Medical students worked with developmental pediatricians to develop a 12 hour elective for preclinical medical students (Years 1 and 2) called "Developing Skills for Developmental Disabilities (DSDD)." This was an optional elective for course credit that consisted of 6 hours didactic sessions and 6 hours of clinical time.
Students received didactic information about disability, peer teaching, practice scenarios, and hands-on time in an inter-disciplinary program for families with children with developmental disability. We developed a 10 question survey rating students' confidence in knowledge and personal comfort when interacting with children with developmental disabilities using a 5 point Likert scale. The students completed the survey at the start and end of the elective. Scores pre- and post-elective were compared.

Results:

22 students signed up for the elective, and 20 students completed all 12 hours. Of these 20 students, 8 had previous work experience with disability, and 11 had personal experience (family or friend related) with disability. A statistically significant (CI 95%) increase in self-reported scores of confidence was seen for 8 out of the 10 questions.

Conclusions:

Overall, the 12 hour DSDD elective was shown to increase confidence in preclinical medical students' ability to interact with children with disabilities and their families. Limitations of the study were unavailability of a previously validated instrument, and small sample size. Also students self-selected to participate, and some already showed interest in disability. Future directions include possibly repeating the study with a control group or assessing whether there is an increase in students' skills, rather than just their confidence.

Funded By:

Abstract #: 156
Presenter: Megan Beggs
Supervisor: R. Todd Alexander
Title: Intestinal calcium absorption throughout development
Authors: Megan Beggs, R. Todd Alexander
Affiliations: University of Alberta
Research Activity: Women and Children's Health: mechanisms of ion transport
Investigation Type: Quantitative Research

Introduction

Calcium is essential to vital physiological functions including bone mineralization where deposition peaks in infancy and content peaks in early adulthood. Children who fail to achieve healthy bone mineralization are at increased risk of fractures and growth failure. Calcium homeostasis is mediated by interactions between the intestine, kidneys, and bones. Intestinal absorption occurs by an active transcellular or by a passive paracellular pathway with similar pathways of reabsorption in the kidneys.

We seek to delineate molecular mechanisms permitting a positive calcium balance throughout development. We hypothesize a transition from predominantly paracellular to transcellular intestinal absorption around the age of weaning.

Methods

Tissues from wild type FVB/N mice (n=12) at 7 age points from one day to 6 months old were snap frozen. RNA was isolated using TRIzol Reagent (Invitrogen) and reverse transcribed into cDNA. Expression levels were quantified using real-time PCR (ABI Prism 7900 HT) with specific primers and probes from IDT. Research is approved by the University of Alberta Animal Care and Use Committee for Health Sciences. One way ANOVA was performed to analyze difference between means using GraphPad Prism 2.0. $p<0.05$ was considered significant.

Results

TRPV6 and $CalbD_{9k}$, mediators of transcellular calcium transport, show a six-fold increase in expression between two weeks and one month of age in the duodenum. Expression of TRPV5 and PMCA1b, mediators of transcellular calcium transport in the kidney, show peak expression at 7 days of age and decline by 50% by 1 month. Mediators of paracellular calcium transport in the kidney show peak expression at 7 days of age and decline by 50% by 1 month.

Conclusions

Preliminary gene expression results suggest that gene expression of the transcellular pathway in the duodenum is markedly increased after the age of weaning suggesting that before this time, the mice are not capable of active calcium uptake in this tissue. Results from gene expression studies in the kidney, however, suggest that there may be compensation to decrease calcium loss prior to the age of weaning.

Future Directions

A) Continue quantitative PCR and immunoblotting expression profiles of known molecular moderators in intestinal segments in wildtype and mice lacking
TRPV6.

B) Ussing chambers studies to directly measure transcellular versus paracellular calcium flux across intestinal segments.

C) MicroCT to assess bone mineralization in both wildtype and KO mice.

D) Quantify expression changes of genes for calcium regulating hormones vitamin D, parathyroid hormone, PTH-related protein, and

calcitonin. Funded By:

women & children's health research institute

Abstract #: 157
Presenter: Samah Damanhoury
Supervisor: Geoff Ball
Title: How is 'Metabolically Healthy Obesity' Defined in Children? Preliminary Findings from a Scoping Review
Authors: Samah Damanhoury, Amanda Newton, Marghalara Rashid, Geoff Ball
Affiliations: University of Alberta
Research Activity:
Investigation Type: Qualitative Research

INTRODUCTION (Purpose): Individuals with metabolically healthy obesity (MHO) are unique despite their high level of adiposity, they do not possess cardiometabolic risk factors often associated with obesity (*e.g.,* insulin resistance, high blood pressure, dyslipidemia). Currently, there is no universal definition of MHO in children or adults, which has led to diverse prevalence estimates. The objective of this scoping review is to determine how MHO is defined in children. This review is ongoing, so herein, we report our progress to date.

METHODS: This review is being conducted according to established scoping review methodology. Our search of seven electronic databases was limited by year (1980 to 2015) and English language literature. Hand-searches were conducted for references and conference proceedings. Primary authors were also contacted. Studies of any quantitative or qualitative design that were conducted with 2-18 year olds were eligible for inclusion. Literature reviews retrieved during the search process were reviewed for potentially eligible primary studies. To be eligible for inclusion, studies needed to include a MHO definition that included all of the following: variables (*e.g.,* LDL-C) and variable cut-offs (*e.g.,* HDL-C >1.03 mmol/L), and the number of criteria used to define MHO (*e.g.,* 0 risk factors). Studies also needed to include BMI-for-age and sex based on established criteria. Two reviewers independently screened studies for inclusion. One reviewer is currently extracting the data on study and participant characteristics as well as data related to MHO definitions; a second reviewer will subsequently check for completeness and accuracy. Extracted data will be summarized quantitatively, and research gaps and needs will be summarized qualitatively. The methodological quality of each study will be assessed using the modified Newcastle-Ottawa Scale.

RESULTS: Our search retrieved 1,309 papers, of which 23 individual studies met our inclusion criteria. We anticipate that data extraction will be completed by October, 2015. Subsequently, quality assessment and data analysis will be completed by December, 2015.

CONCLUSION: Our scoping review was designed to examine the volume and variability of MHO definitions applied in pediatric research. Documenting key knowledge gaps and future research directions will help to advance this field of research, which should include the development of a universal definition of MHO for children.

Funded By: Umm AlQura University Makkah,SA

Abstract #: 158
Presenter: Stephen Hunter
Supervisor: Valerie Carson
Title: How can schools impact student physical activity? A longitudinal assessment of school initiatives in the COMPASS study
Authors: Stephen Hunter, Valerie Carson, Scott Leatherdale
Affiliations: University of Alberta
Research Activity: Physical activity and sedentary behaviour of children and youth
Investigation Type: Quantitative Research

Introduction

A large proportion of school-aged Canadians are not active enough to achieve optimal health benefits. Furthermore, there is a noticeable decline once children enter their high school years. In response, the cohort study for obesity, marijuana use, physical activity, alcohol use, smoking, and sedentary behaviour (COMPASS) works with secondary schools to evaluate current health behaviours and design strategies to improve student health. The purpose of this research is to examine the impact that changes to school policies, resources, programs, and the physical environment have on student physical activity over a 1 year period.

Methods

As part of a quasi-experimental study design, this research includes approximately 50,000 students (grade 9-12) and 89 administrators from a sample of 89 secondary schools in Ontario and Alberta, Canada enrolled in the COMPASS study. COMPASS is a prospective cohort study that administers annual student and administrator questionnaires, and collects data on the physical environment. Data from student questionnaires is used to create school health profiles.
Knowledge brokers then work with administrators on a yearly basis to develop and implement strategies to enhance student health. Changes to policies, resources, and programs are measured through several questions in the administrative questionnaire. Changes to the school physical environment are measured with previously validated software that allows pictures and facility rankings to be collected during school audits. Physical activity is measured with valid and reliable questions from the student questionnaire. Multi-level modeling will be used to compare student's physical activity participation between schools that have and have not implemented changes to policies, resources, programs, and the physical environment.

Discussion

This study will fill an important gap in the literature by providing insight into what school-based initiatives are most effective for increasing physical activity in a large, longitudinal sample of Canadian youth. Identifying an effective and sustainable approach for increasing physical activity through schools is essential for reversing the low physical activity participation of Canadian youth. Increasing the proportion of Canadian students who meet the recommended amount of physical activity will result in improved physical and psychosocial health, reductions in chronic disease risk, and improvements in quality and longevity of life.

Funded By: Graduate Studentship

Abstract #: 159
Presenter: Orysya Svystun
Supervisor: Hamdy El-Hakim
Title: Swallowing dysfunction in healthy children; characteristics and management of a consecutive cohort at a tertiary centre
Authors: Orysya Svystun, Wendy Johannsen, Rabin Persad, Justine Turner, Carina Majaesic, Hamdy El-Hakim
Affiliations: University of Alberta
Research Activity: Pediatric swallowing dysfunction
Investigation Type: Quantitative Research

Introduction

Swallowing dysfunction (SD) is a common complaint. Its complications can be particularly debilitating in children, who may as a result fail to thrive. Since swallowing relies on precise neuromuscular coordination, patients with neurological impairments, structural abnormalities, or syndromes are particularly at risk. Consequently, most of the research on pediatric SD has focused on these populations, leaving apparently otherwise healthy children under-investigated. We report the parameters of otherwise healthy children with SD and airway compromise consecutively evaluated at a tertiary center.

Methods

This was a retrospective study of patients attending a tertiary multi-disciplinary aspiration clinic over 31 months. Children (≤17 years) without neurological, genetic, or other major system disorder had their files reviewed. The collected data (includes presenting symptoms, risk factors, developmental status, swallowing assessment results, and interventions) was analyzed using descriptive statistics.

Results

One hundred and twenty-six patients with complete records met inclusion criteria (71 boys, mean age 16.7±22.8 months (0.5-124.2)). The majority presented with choking on liquids or solids and congestion during feeding (24 recurrent pneumonia, 13 cyanotic spells, nine life-threatening events). Premature birth was present in 26 and failure to thrive in nine. At baseline assessments (65 endoscopic evaluation of swallowing, 74 modified barium swallows) 69 demonstrated laryngeal penetration, 23 aspiration (silent in 21). Seventy had a pulse oximetry test, 75 underwent laryngoscopy & bronchoscopy, and 26 gastrointestinal endoscopy. Findings included laryngomalacia (27), laryngeal mobility disorder (7), laryngeal paralyses (4), and subglottic stenosis (5). Surgical interventions included supraglottoplasties (17), endoscopic laryngeal cleft repairs (17), and laryngeal cleft injection augmentations (27). Medical interventions included modified oral diet (83) and tube feeding (15). At the latest follow-up (mean 11.5±12.1 months (0.3-88.8)) 99 responded to management (53 total symptom resolution; 47 resumed normal diet or reduced thickening).

Conclusions

Thus far, this is one of the largest studies documenting the parameters of healthy children with SD. Over half of these children had anatomical abnormalities which are potentially amenable to surgical solutions and a significant proportion exhibited major signs of SD on instrumental studies that required active intervention. Furthermore, upon inquiry nearly half snored on a regular basis. This study provides information on a previously under-investigated population and includes an insight into the multi-disciplinary resources required.

Funded By: Wynne Rigal Summer Research Award - University of Alberta

women & children's health research institute

Abstract #: 160
Presenter: Kristie DeHaan
Supervisor: Joanna MacLean
Title: Exploring the impact of intrauterine growth restriction on breathing in early life
Authors: K DeHaan, JE MacLean
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Lung Development
Investigation Type: Quantitative Research

Introduction: Intrauterine growth restriction (IUGR) is associated with impaired lung function and increased respiratory morbidity from infancy through adulthood. While IUGR was previously thought to be protective for early respiratory disease by enhanced lung maturation, animal studies document changes in surfactant, alveolarization and airway function. Adaptation to respiratory abnormalities may manifest as changes in respiratory patterns, including apnea, and altered response to changes in oxygen and carbon dioxide. The aim of this study is to explore the impact of IUGR on respiratory patterns and response to changes in oxygen using data collected during clinical care.

Methods: This is a retrospective chart review of physiological data collected during limited channel sleep studies collected in the Neonatal intensive care unit (NICU). The population for this study include 804 infants who underwent sleep study while in the NICU. Respiratory pattern, oxygen saturation and heart rate were recorded during testing. Infants born IUGR were matched for gestational age and sex to an infant born with weight appropriate for gestational age (AGA). Birth history, NICU chart data, and sleep studies were reviewed.

Results: Infants with IUGR comprised 7.5% of the original cohort from which 39 matched IUGR-AGA pairs with complete data were identified. Gestational age was similar (IUGR 33.8±4.5 weeks; AGA 33.8±4.5 weeks, p=ns) while birth weight differed by approximately 840g (IUGR 1636±788g; AGA 2477±940g, $p<0.01$). Mothers of infants born IUGR were less likely to received antibiotics prior to delivery (IUGR 28%; AGA 51%, $p<0.05$) while more infants born IUGR had physical anomalies (IUGR 54%; AGA 15%, $p<0.01$). Infants born IUGR were discharged from the NICU at a later gestational age (IUGR 40.9±4.0 weeks; 38.8±2.8 weeks, $p<0.05$) and were more likely to be discharged on oxygen (IUGR 36%; AGA 13%, $p<0.05$). Age at sleep study was similar between the group (IUGR 54±39 days; AGA 43±35 days, p=ns). Preliminary analysis of the sleep study data show similar heart rate, oxygen saturation and periodic breathing events profiles between groups but shorter duration of the longest central apnea in infants born IUGR (10.4±3.8s vs 12.2±3.6s, $p<0.05$).

Conclusion: We have established a cohort of 39 IUGR-AGA matched pairs for whom respiratory measurements were recorded during their NICU admission. Preliminary analysis demonstrates longer length of stay, greater oxygen use on discharge despite shorter duration of the longest central apnea in infants born IUGR. Future analyses of the sleep study data will explore differences in respiratory patterns and oxygen response.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 161
Presenter: Rhonda Rosychuk
Supervisor:
Title: Differences in emergency department visits for asthma: Does sex matter?
Authors: Rhonda Rosychuk, Jingbin Zhang, Richard Leigh, Andrew Cave, Maria Ospina, Brian Rowe
Affiliations: University of Alberta
Research Activity: Respiratory diseases
Investigation Type: Quantitative Research

Introduction

Asthma is a common chronic respiratory disease for children and adults worldwide. Exacerbations of asthma are common and frequently result in visits to emergency departments (EDs). This study examines sex differences in outcomes for patients discharged from the ED after an asthma presentation in Alberta, Canada.

Methods

A cohort of Alberta residents aged ≤ 55 years who presented to one of 104 EDs with asthma during April 1999 to March 2011 was identified from provincial administrative health databases. Time to first follow-up visit to a physician and the probability of ED return for asthma within 30 days after discharge was modelled using Cox proportional hazards and logistic regression models, respectively. Models included indicators for pediatric (age < 18 years) and adult (age 18 to 55 years) groups.

Results

There were 129,853 patients/ED presentations analyzed (39.3% and 59.1% female in pediatric and adult groups, respectively); with most being discharged (38.2% and 59.8% female in pediatric and adult groups, respectively). Approximately 26% of discharged patients returned to the ED for asthma during the study period and 5.2% patients returned within 30 days. Women had significantly higher odds of ED return within 30 days than men (unadjusted odds ratio [uOR]=1.26; 95% confidence interval [CI] 1.17 to 1.36); however, a sex difference was not observed for the pediatric group (uOR=0.99, 95% CI: 0.92 to 1.06).
After adjusting by important variables, statistically significant interactions between sex, age, social economic status proxy, and prior claim for were identified that changed the effect of sex on ED return for both the pediatric and adult groups. Similarly, the time to first physician follow-up visit was shorter for both girls and women (unadjusted hazard ratio [uHR]=1.02; 95% CI: 1.01 to 1.04, uHR=1.61; 95% CI: 1.58 to 1.63, respectively). After adjusting by important variables, statistically significant interactions between sex and age, socio-economic groups, zone of residence, prior asthma claim, and comorbidity score were identified that changed the effect of sex on time to physician follow-up for both the pediatric and adult groups.

Conclusions

Our study identified sex differences in the odds of ED return within 30 days of discharge for adults with acute asthma and showed that time to first physician follow-up for both pediatric and adult groups differed by sex. Multiple factors contribute to these differences and further study is required to better understand the reasons for the differences.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 162
Presenter: Yong Zhang
Supervisor: Gregory Funk
Title: The Secondary Hypoxic Depression of Breathing In Vitro Is Attenuated by ATP Acting via PLC/IP3-Dependent Excitation of Inspiratory Neuron
Authors: Yong Zhang, Alexander Gourine, Sergey Kasparov, Tucaaue Alvares, Gregory Funk
Affiliations: University of Alberta
Research Activity: Child and Youth Development : Sleep and Breathing Disorders
Investigation Type: Quantitative Research

Introduction: The ventilatory response to hypoxia comprises an initial increase in ventilation followed by a secondary depression that can be life-threatening in premature infants. ATP released within the ventral respiratory column, including the preBötzinger Complex (preBötC, critical site for inspiratory rhythm generation), during hypoxia attenuates this depression. The site(s) and mechanisms via which ATP mediates this action are not known. Our working hypothesis is that hypoxia stimulates ATP release from preBötC astrocytes and that the ATP depolarizes local inspiratory neurons in a $P2Y_1$ receptor (R)-dependent manner to increase inspiratory frequency (freq). The goals of my study were first to identify the signaling pathways through which ATP excites the rhythm-generating network and second to determine if the ATP released in hypoxia causes glial cells to release the excitatory transmitter, glutamate, which would further increase breathing.

Methods: I used a well-established in vitro model in which the inspiratory rhythm generating network, the preBötC, is isolated in a dish where it continues to generate rhythm. Inspiratory network activity was recorded from XII nerves and the activity of inspiratory preBotC neurons was recorded via whole-cell recording techniques, before and after addition of second messenger blockers and ionotropic glutamate receptor antagonists to the slice or into single neurons.

Results: Bath application of PPADs and Suramin potentiated the anoxia-induced depression in inspiratory-related activity in vitro, confirming that even in vitro ATP is released within the respiratory network to attenuate the secondary respiratory depression induced by anoxia. Bath application of the PLC blocker, U73122, shortened the duration of MRS2365-evoked frequency increase without affecting its peak magnitude, while 2-APB, an inositol trisphosphate (IP_3) receptor inhibitor, reduced the freq increase by 63%. In contrast intracellular dialysis of U73122 and 2-APB attenuated the ATP-induced inward currents in inspiratory neurons by 50±7% and 42±17%, respectively. Bath application of U73122 had no effect on the ATP-induced inward current, suggesting U73122 in the bath does not access the neurons. To determine if ATP causes astrocytes to release glutamate and excite inspiratory neurons, I compared neuronal ATP currents before and after applying AP5 and CNQX in the presence of TTX. AP5 and CNQX had no effect on the ATP current.

Conclusion: These data suggest that ATP is released during anoxia in vitro and that it attenuates the magnitude of the secondary respiratory depression by activating PLC and IP_3 signaling cascades in inspiratory neurons.

Funded By: Graduate Studentship

women & children's health research institute

Abstract #: 163
Presenter: Eric Parent
Supervisor: Eric Parent
Title: Is Posture Affected by Rotation of the Vertebrae in Adolescent with Idiopathic Scoliosis? A Surface Topography Validity Study.
Authors: Eric C. Parent, Emily Redford, Sheri Schmidt, Douglas Hill, Marc Moreau, Douglas Hedden, Samer Adeeb, Edmond Lou
Affiliations: University of Alberta
Research Activity: Child and Youth Development: Musculoskeletal health
Investigation Type: Quantitative Research

Introduction: Scoliosis is a 3D spine deformity characterized by lateral curvature and vertebral rotation. radiographs are routinely used to assess internal deformities but can be harmful. Surface topography assesses external deformities non-invasively. Few studies have examined the association between surface and radiographic measurements of rotation and prior studies have often yielded disappointing results. However, this may be due to combining patients with different curve types. The goal of this study was to compare the associations between rotation measurements obtained using surface topography and radiograph measurements among curve types.

Methods: A total of 263 volunteer patients with adolescent idiopathic scoliosis were recruited consecutively from our scoliosis clinic. Selection criteria were: age 10 to 18 years old, able to stand unassisted for two minutes, without trauma or co-morbidities affecting external deformities. All participants had a radiograph and a full-torso surface topography scan taken during the same visit while standing in a standard position. Fifteen landmarks were digitized to extract nine surface parameters quantifying torso rotation using custom Matlab software. Vertebral rotation was measured on radiographs using SpineTestEx using Stokes method after selecting the apical vertebra, identifying the pedicles and the edges of the vertebral body. Pearson Correlation Coefficients were used to quantify associations between surface and radiograph measurements.

Results: Combining curves types there were 263 participants aged 14.3 ± 1.8 years; 48 had a single thoracic curve, 39 a single lumbar curve and 89 a double curve. Correlation coefficients when combining all patients ranged from 0.07 to 0.48 (angle between the principal axis of inertia of torso cross-sections and the frontal plane). Correlations when focusing on single thoracic curves were larger and ranged between 0.14 and 0.73 (Hump Sum). Correlations in the subgroup with single lumbar curves were also larger than the overall group ranging between 0.09 and 0.54 (Global apparent asymmetry). Correlations in those with double curves were not larger than the overall group ranging between 0.11 and 0.37 (HumpSum). Depth difference at the shoulders had the weakest correlation for all curve types.

Conclusion: As hypothesized, separating curve type subgroups allowed for observing stronger correlations between surface measurements and vertebral measurements of rotation. Lumbar curves led to mixed results, perhaps because the effect of vertebral rotation may be masked by the soft tissue. Surface topography can provide valid rotation measurement especially in those with thoracic curves possibly because vertebral rotation displaces the ribs which affects the surface more directly.

Funded By: Innovation Grant

women & children's health research institute

Abstract #: 164
Presenter: Xin Wang
Supervisor: Neelambar Kaipatur
Title: Methods to measure alveolar bone and lower incisor inclination using CBCT: a preliminary study
Authors: Xin Wang, Neelambar Kaipatur, Kim-Cuong Nguyen, Paul Major, Lawrence Le
Affiliations: University of Alberta
Research Activity: Dental
Investigation Type: Qualitative Research

Introduction

Cone beam computed tomography (CBCT) is a medical imaging modality involving ionizing radiation. The CBCT scanner has an X-ray tube and a flat panel detector on the opposite side of the X-ray tube, which rotate around the target in synchronization. The tube generates divergent X-ray to penetrate through the target and the transmitting photons are intercepted by the detector. Three-dimensional images can be reconstructed using the two-dimensional digital images acquired at discrete angular positions. The resolution of CBCT images is superior to that of the intra-radiographs at the expense of higher radiation exposures. CBCT has found many applications in dental implant placement, orthodontics, and temporomandibular joint imaging.

In orthodontics, assessment of alveolar bone plays an important role, as the thickness of alveolar bone defines the boundaries of orthodontic movement. Tooth movement beyond these boundaries may result in problems such as fenestration, dehiscence, root resorption, and gingival recession, which lead to periodontal diseases. This is especially important for those individuals with Angle Class II malocclusion, often accompanied by a sagittal retrognathism of the mandible. The method is to forward positioning the mandible, to achieve the desired dental and skeletal changes especially in lower incisor region and the accompanying periodontal effects, which are often measured using CBCT. However there are many methods described in the published literature to measure changes in the region of lower incisor inclination and alveolar bone level.

The main objective of the project is to find an accurate and reliable method among all existing methods to evaluate the changes in alveolar bone and the inclination of the lower incisors and apply it to our existing CBCT data. The present study is related to the first phase of the project, which is to review current literature.

Methods

A broad literature search was conducted on PubMed and Google Scholar with combinations of the following search terms: CBCT, Angle Class II malocclusion, methods, measurement, alveolar bone, lower/mandibular incisors. Relevant articles were collected, and their references were hand-searched to identify more articles.

Results

The important parameters of measurement have been identified: height of the alveolar bone, thickness of the alveolar bone, and inclination of the lower incisors. All existing methods used one parameter or any combination. This study provides a critique of the existing methods and outlines their measurement objectives.

Conclusion

The success of identifying a reliable and accurate method will significantly improve patient care in pediatric and adolescent orthodontic

patients. Funded By: China Scholarship Council, CIHR

women & children's health research institute

Abstract #: 165
Presenter: Schammim Ray Amith
Supervisor: Larry Fliegel
Title: Regulation of Na+/H+ exchange in triple-negative breast cancer metastasis
Authors: Schammim Ray Amith, Jodi Wilkinson, Larry Fliegel
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Quantitative Research

Introduction: The leading cause of fatality in patients with breast cancer is metastasis. Triple-negative breast cancer (TNBC) is a clinical breast cancer subtype that occurs in 15-20% of patients. It is aggressively metastatic, has high recurrence rates, low responsiveness to chemotherapy, and poor prognoses for survival.
Currently, no targeted therapies against TNBC exist, so finding novel avenues to fight this disease is imperative. The key pathophysiological role of the Na^+/H^+ exchanger NHE1 in tumour progression has become clearer in recent years. Therefore, the manipulation of pH homeostasis and Na^+/H^+ exchange in the tumour microenvironment is now being considered as an anti-cancer therapeutic strategy.

Methods: We generated an NHE1-knockout of the triple-negative MDA-MB-231 breast cancer cell line. Wild-type (wtNHE1) and mutant NHE1 protein was then reintroduced into these NHE1-knockout cells to determine the role of NHE1 regulation on TNBC metastasis. We investigated the effect of changes to NHE1 regulation by: $p90^{RSK}$/14-3-3 (S703A), ERK1/2 (S766,770,771A or SSSA), and calmodulin (K641R643,645,647E or 1K3R4E). To assess the effect of mutations to NHE1 on the metastatic potential of MDA-MB-231 cells, rates of cell migration, invasion and colony growth were analysed. Migration rates were a measure of time to gap closure in wound-healing assays. Transwell invasion assays were used to guage cell invasion rates through a Matrigel® matrix. Colony formation was evaluated by anchorage-dependent growth, growth in soft-agar (anchorage-independent) and spheroid growth in Matrigel® matrix.

Results: S703A cells showed a dramatic difference in morphology, becoming smaller and reverting from a mesenchymal to an epithelial-like phenotype with a concomitant loss of expression of mesenchymal marker vimentin. Compared to cells expressing wtNHE1, S703A cells had significantly lower rates of migration, invasion, anchorage-dependent and -independent colony formation, and spheroid growth. Migration and colony formation of SSSA cells were also adversely affected by interfering with the activation of NHE1 by ERK1/2, but invasion and spheroid growth were not. The 1K3R4E mutant, where NHE1 auto-inhibition and its ability to bind calmodulin were negated, had much higher rates of migration, invasion and spheroid growth.

Conclusions: Our data demonstrate a novel link between epithelial-mesenchymal transition and NHE1 regulation that is likely dependent on $p90^{RSK}$-mediated signalling downstream of ERK1/2, and the binding of 14-3-3. We suggest that Ser703-NHE1 is a critical phosphorylation switch that regulates epithelial- mesenchymal transition in TNBC cells, and is thus a promising target for the development of new chemotherapies.

Supported by the Canadian Breast Cancer Foundation and WHCRI.

Funded By: Innovation Grant

Abstract #: 166
Presenter: Mackenzie Coatham
Supervisor: Lynne-Marie Postovit
Title: Linking Mutations to BRG1 to Aggressive Dedifferentiated Endometrial Carcinoma
Authors: Mackenzie Coatham, Xiaodong Li
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type:

Introduction: Brahma-related gene 1 (BRG1), one of the core catalytic subunits in the eukaryotic SWI/SNF chromatin remodeling complex has been implicated in a variety of biological processes. As an ATP-dependent helicase, BRG1 is often considered a transcriptional coactivator and under different microenvironmental triggers like hypoxia, BRG1 can amplify cellular responses to environmental stimuli and produce phenotypical changes such as epithelial to mesenchymal transition (EMT) that are required for cellular adaptation. Biallelic inactivation of BRG1 as result of nonsense, frameshift and splice site mutations has been reported in non-small cell lung cancer (NSCLC) and small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Both NSCLC and SCCOHT share a common rhabdoid phenotype featuring macronuclei and eosinophilic cytoplasm. Recently, endometriod adenocarcinomas displaying an undifferentiated, large cell, rhabdoid phenotype have been discovered and reported to be BRG1-deficient. This dedifferentiated endometrial carcinoma (DDEC) is a highly aggressive type of endometrial cancer. Understanding the contribution of BRG1 inactivation to the DDEC phenotype and biology, will allow for targeted therapy to be developed against the unique molecular features of this cancer. This study could also provide insight into how BRG1 inactivation, at the transcriptional and epigenetic level, maintains undifferentiated gene expression programs in other cancers such as NSCLC and SCCOHT. Methods: Targeted sequencing together with immunohistochemistry was utilized to detect mutations and loss of BRG1 in clinical cases of DDEC. Established human endometrial cancer cell lines were characterized for their level of BRG1 expression by pairing immunofluorescence studies with Western blot analysis. The expression of EMT and stem cell-related genes in these cells lines was determined using qRT-PCR. Results: Close to 40% of clinical cases of DDEC show a loss of BRG1 with the majority having developed in a mismatch repair protein-deficient molecular context. Most of the highly microsatellite unstable, hypermutated (MSI-high) endometrial cancer cell lines expressed BRG1 at low levels. Interestingly, most MSI-high endometrial cancer cell lines retained an epithelial-like phenotype, expressing high levels of E- cadherin. Conclusions: These results lay the foundation for developing an in vitro model of DDEC using current CRISPR technology to knockout BRG1 in MSI-high endometrial cancer cell lines. Direct comparison between the in vitro derived human DDEC model and patient derived xenograft (PDX) models from clinical DDEC cases will be critical to our understanding of the role of BRG1 in cellular dedifferentiation at the genetic, epigenetic and molecular level.
Funded By:

women & children's health research institute

Abstract #: 167
Presenter: Jarod Li
Supervisor: Lynne Postovit
Title: Estrogen induces Nodal in luminal-like breast cancer cells and Nodal reciprocally silences ER alpha expression
Authors: Jarod Li, Padmalaya Das, Lynne Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Mixed Methods

Introduction

Estrogen plays a key role in the in the normal growth and development of the breast and is also a major contributor to breast cancer growth. Recent studies have demonstrated that embryonic morphogen, Nodal is expressed in metastatic breast cancers and that its expression is correlated with breast cancer progression. In silico analyses suggest that there are several putative ER-binding sites in proximity to the Nodal coding region.

Methods and results

We herein reveal that stimulation of MCF-7 and T47D breast cancer cell lines (that are estrogen receptor positive and express low levels of Nodal) with estradiol (E2) increases Nodal protein levels. Treatment with the ER antagonist, ICI 182,780 abrogates the E2-enhanced Nodal protein expression. Conversely, treating these cells with recombinant Nodal resulted in a decreased expression of estrogen receptor in these cells both at the transcript and protein levels, suggesting a bidirectional interaction between estrogen receptor and Nodal in these cell lines. In addition, our results show miRNA 145 is downregulated post treatment with E2 in MCF7 cells and this effect of estrogen on the miRNA is reversed with treatment with ICI. Indeed, Nodal protein expression is largely reduced in the presence of miRNA 145 mimics and is enhanced when miRNA expression is inhibited using a miRNA 145 inhibitor.

Conclusions

Our results support the hypothesis that E2 positively regulates Nodal expression in breast cancer tissues through repressing miRNA145. Future experiments are aimed at understanding in depth the regulatory mechanisms and biological functions governing E2-induced Nodal, to provide better insight into hormonal regulation in metastatic breast cancer.

Funded By:

women & children's health research institute

Abstract #: 168
Presenter: Jiahui Liu
Supervisor: Lynne-Marie Postovit
Title: Ovarian Cancer Biomarker CA125 Expression is Attenuated in in vitro Culture
Authors: Jiahui Liu, Helen Steed, Yangxin Fu, Cheng-Han Lee, Guihua Zhang, Krista Vincent, Dylan Dieters-Castator, Desmond Pink, John Lewis, Lynne-Marie Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Mixed Methods

Introduction: CA125, a 22,152 amino acid protein encoded by *MUC16*, is a glycoprotein that is used as a biomarker for ovarian cancer. Approximately 80% of ovarian cancer patients present with high levels of serum CA125. Overexpression of this biomarker in ovarian cancer indicates its possible role in cancer pathogenesis; however studies related to CA125 function in cancer development are quite limited. During our research on biomarkers we found that only one out of seven ovarian cancer cell lines (NIH:OVCAR3) expresses CA125. Accordingly, we hypothesized that CA125 may be lost during adaptation to cell culture conditions. **Methods:** We studied CA125 in cell lysate, microvesicles and supernatant in ovarian cel lines and patient ascites cells by Western blot and PCR. In support of this concept, analysis of publicly available data sets, including The Cancer Genome Atlas (TCGA) revealed that while the majority of primary ovarian cancer sample express high levels of MUC16, only three out of fifteen ovarian cancer cell lines express appreciable amounts. **Results:** We confirmed this result by demonstrating that CA125 could not be detected in the cell lysates, microvesicles or supernatants of six ovarian cancer cell lines (A2780s, A2780cp, SK-OV3, OV-90, ES-2 and OVCA429). It could, however, be detected in all fractions from OVCAR3 cells. Four of ten cultured ascites cells from ovarian cancer patients, whose clinical CA125 levels were above 35 kU/L, showed detectable CA125 by Western blot. In contrast, CA125 could be in detected in almost all lysates, microevesicles and supernatants derived from ascites that had never been cultured. In order to determine if CA125 was indeed lost over time, we compared CA125 protein and mRNA levels in primary ovarian cancer cells before and after successive passages. We determined that both transcript and protein were lost as early as one passage in culture. Notably, we insured that we were culturing ovarian cancer cells (and not contaminating stromal cells) with sequencing for mutations as well as Western blotting for the epithelial ovarian cancer markers Cytokeratin 7 (CK7) Cytokeratin 20 (CK20) and Estrogen Receptor (ER).
Conclusions: Taken together, our results indicate that ovarian cancer cells rapidly lose the expression of CA125 as they are adapted to in vitro culture conditions. Hence, caution should be used when using cell lines for biomarker discovery.

Funded By:

women & children's health research institute

Abstract #: 169
Presenter: Kaitlyn Lopushinsky
Supervisor: Lynne-Marie Postovit
Title: Exploring the functional link between Epithelial Splicing Regulatory Protein 1 and Dystonin isoforms associated with breast cancer prognosis
Authors: Kaitlyn Lopushinsky, Scott Findlay, Krista Vincent, Lynne-Marie Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Quantitative Research

Introduction: In 2015, it is estimated that 25,000 women will receive a breast cancer diagnosis and 5,000 will die. To understand which genes affect breast cancer survival the most, we used the Cancer Genome Atlas patient survival and paired gene expression data and found that high expression of epithelial splicing regulatory protein 1 (ESRP1) was highly associated with poor patient survival. ESRP1 controls the epithelial status of cells, which is associated with metastasis, specifically through regulation of alternative splicing events. We then looked for gene isoforms which correlated with ESRP1 as well as patient survival. Two isoforms (named dxl and zay) of the gene dystonin (DST) correlate with patient survival and ESRP1. DST is a plakin family protein important for plaque adhesion junctions of hemidesmosomes.

Methods: The objective was to measure endogenous levels of ESRP1 and the two DST isoforms in normal breast and breast cancer cell (BCC) lines and then determine if ESRP1 knockout affects DST isoform expression. PCR products were sequenced to validate DST isoform expression before quantification using digital droplet PCR (ddPCR). Clustered Regularly Interspaced Palindromic Repeats (CRISPRs) were utilized to generate ESRP1 mutations.

Results: ESRP1 and zay levels showed no difference between normal breast and BCC lines. However, we found that dxl showed significantly higher expression in normal breast lines than BCC lines. Successful CRISPR-induced ESRP1 mutations were determined using a ddPCR mutation assay and confirmed by sequencing.

Conclusions: Our results showed that DST dxl is more highly expressed in normal breast cell lines as predicted by bioinformatics. There is no significant difference between normal breast and breast cancer cell expression of DST zay. ESRP1 mutations were confirmed through a ddPCR mutation assay and successful clones were screened and sequenced. Single cell clones will be screened for ESRP1 knockout. This project will be used to determine if there is a functional link between ESRP1 and DST in breast cancer metastasis.

Funded By: ACF

women & children's health research institute

Abstract #: 170
Presenter: Krista Vincent
Supervisor: Lynne Postovit
Title: Expression of ESRP1 is a novel indicator of poor prognosis in breast cancer patients
Authors: Krista Vincent (*co-first author), Scott Findlay (*co-first author), Lynne Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Quantitative Research

The genetic alterations contributing to breast cancer pathogenesis are incompletely defined, and identifying independent prognostic features from large sample, genome-wide datasets remains a goal of current research. We used transcriptome profiling of 1062 primary breast cancers and 113 associated normal samples from the The Cancer Genome Atlas (TCGA) to find gene expression associated with breast cancer development and progression. This bioinformatics screen revealed that Epithelial Splicing Regulatory Protein 1 (*ESRP1*) is expressed at significantly higher levels in primary breast cancer samples compared to normal tissue, and its expression is associated with poor prognosis in discovery and validation patient cohorts (Hazard ratio(HR)=1.88, p=0.001 and HR=1.42, p<0.001). Analysis of copy number changes showed that *ESRP1* had a gain or amplification in 45% and 16%, respectively, of patient samples; copy number status was also significantly positively associated with *ESRP1* expression. Correlation network analysis revealed specific and novel transcript splice variants that are linked with *ESRP1* expression. This includes two variants of dystonin (*DST*), a member of the plakin protein family of adhesion junction plaque proteins, that have opposite associations with patient survival. We are using a CRISPR-mediated gene editing approach to introduce missense mutations into the *ESRP1* locus to generate luminal breast cancer cell lines with functional knockouts of ESRP1. We will determine if there is a causal link between ESRP1 and the differential expression of the correlated *DST* isoforms. We will also examine if functional knockout of ESRP1 *in vitro* reduces aggressive phenotypes such as proliferation and invasion. Our study demonstrates that high *ESRP1* expression can serve as an independent predictor of survival in breast cancer, and aims to determine if ESRP1 can functionally promote breast cancer progression.

Funded By:

women & children's health research institute

Abstract #: 171
Presenter: Guihua Zhang
Supervisor: Lynne-Marie Postovit
Title: The Effects of Nodal on Human Fibroblast Activation
Authors: Guihua Zhang, Matthew Piaseczny, Scott Findlay, Michael Jewer, Krista Vincent, Jiahui Liu, Lynne-Marie Postovit
Affiliations: University of Alberta
Research Activity: Women's Health : Oncology
Investigation Type: Mixed Methods

Introduction: Metastasis is the main cause of cancer death for breast cancer patients. However, the causative factors and the mechanisms by which cancer cells spread and metastasize remain unclear. Some studies have shown that activation of cancer associated fibroblasts (CAFs) may be pivotal in providing the microenvironment favoring tumor progression and metastasis. In comparison to healthy fibroblasts, CAFs express alpha-Smooth Muscle Actin (a-SMA), some Desmin and Connective Tissue Growth Factor (CTGF) concomitant with increased invasion, migration, and proliferation. Studies from our research team and others have demonstrated that Nodal, a secreted embryonic morphogen, promotes breast cancer tumorigenesis, and is present in the stroma. We herein hypothesize that Nodal causes the activation of stromal fibroblasts toward an activated phenotype. **Methods:** We tested this hypothesis by exposing primary human foreskin fibroblast (HFF) to recombinant human Nodan (rhNodal) for varying periods of time and at varying concentrations by Wstern blot and qPCR. **Results:** Western blotting of lystaes derived from HFF cells exposed to Nodal for 1hour, demonstrated that ERK1/2 and SMAD2/3 are both phosphorylated in response to Nodal. These results demonstrate that HFF can respond to Nodal. A-SMA protein levels (measured with Western blotting) were elevated in HFF treated with Nodal for 3 days, and this increase lasted between 48 to 72 hours after the Nodal containing medium was removed. Accordingly, RT-PCR analysis showed a dramatic increase in the expression of a-SMA and CTGF, with less prominent increases of other fibroblast activation markers, such as Desmin, in HFF cultured in the presence of Nodal. Using Boyden chamber assays, we determined that Nodal promotes HFF cell migration and invasion dose dependently between 0ng and 100ng Nodal; and cell counting following Trypan blue exclusion showed that Nodal causes a modest increase in HFF proliferation. **Conclusions:** Collectively, this data suggests that Nodal induces fibroblast activation. Future studies will examine the consequence of this activation on breast cancer metastasis.

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