Health Related Quality of Life and its determinants in Survivors of Pediatric Stroke

by

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Abstract

The incidence of pediatric stroke has risen to >3.0/100,000. Neurological deficits are witnessed in 70-75% of survivors of pediatric stroke and may influence their health related quality of life (HRQL). A cross sectional study was conducted to evaluate the HRQL of pediatric stroke survivors. Parents of children diagnosed with pediatric ischemic stroke between January 2003 and June 2012 were approached. HRQL was evaluated using self (5-18 years) and proxy report (2-18 years) versions of the Pediatric Quality of Life Inventory (PedsQL 4.0) and compared to reference norms. Ninety children were enrolled. Both parents and children expressed concerns in physical and psychosocial domains of HRQL and identified HRQL of children to be lower than reference norms ($p<0.001$). However, parents reported more impairment and differed in their assessment compared to their children's self-report. The study findings have implications regarding our approach to the overall well being of children with stroke.

Preface

This thesis is an original work by Satvinder Kaur Ghotra. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Health Related Quality of Life and its Determinants in Survivors of Pediatric Stroke”, No. Pro00022728, August 2, 2011.

Dedication

This work is dedicated to all children and families who have been impacted by pediatric ischemic stroke.

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Chapter One: Introduction

With the extensive developments in diagnostic and therapeutic fields, pediatric stroke is far increasingly recognized. Pediatric stroke is also acknowledged as the leading cause of hemiplegic cerebral palsy in children (Lynch, 2009). Despite the prominence of stroke in children, there is a remarkable paucity of research into this important lifelong disability. Importantly, little is known about how stroke in infancy and childhood impact the health related Quality of Life (HRQL) of affected children and their families. The aim of this study was to systemically evaluate the HRQL and its determinants in a pediatric ischemic stroke population.

Pediatric Stroke

Stroke is defined by the World Health Organization (WHO) as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (Aho et al., 1980; WHO MONICA Project Investigators, 1988). In simple terms, stroke can be defined as a neurological injury caused by the occlusion or rupture of cerebral blood vessels. Stroke is the second most frequent cause of death and the third leading cause of disability-adjusted-life-years in adults worldwide (Lozano et al., 2012; Murray et al., 2012). However, stroke is also acknowledged as an important disease in children. Stroke in pediatrics occurs across an age spectrum that includes not only infants and children, but also the developing brain of the fetus and newborn. Stroke is 17 times more common in the perinatal period than later in childhood or beyond (Wu et al., 2005). The perinatal period is recognized as one of the most vulnerable times in life to suffer a stroke. With an incidence ranging between 1 in 1600 to 1 in 5000 live births, the ischemic perinatal stroke has been established as the leading known case of cerebral palsy (Lynch, 2009; Raju et al., 2007; Nelson, 2007). Unlike stroke in adults, the diagnosis of a pediatric stroke is based on neuroradiological confirmation of a vascular event rather than typical clinical presentation of stroke, which is often absent in the case of a perinatal stroke.

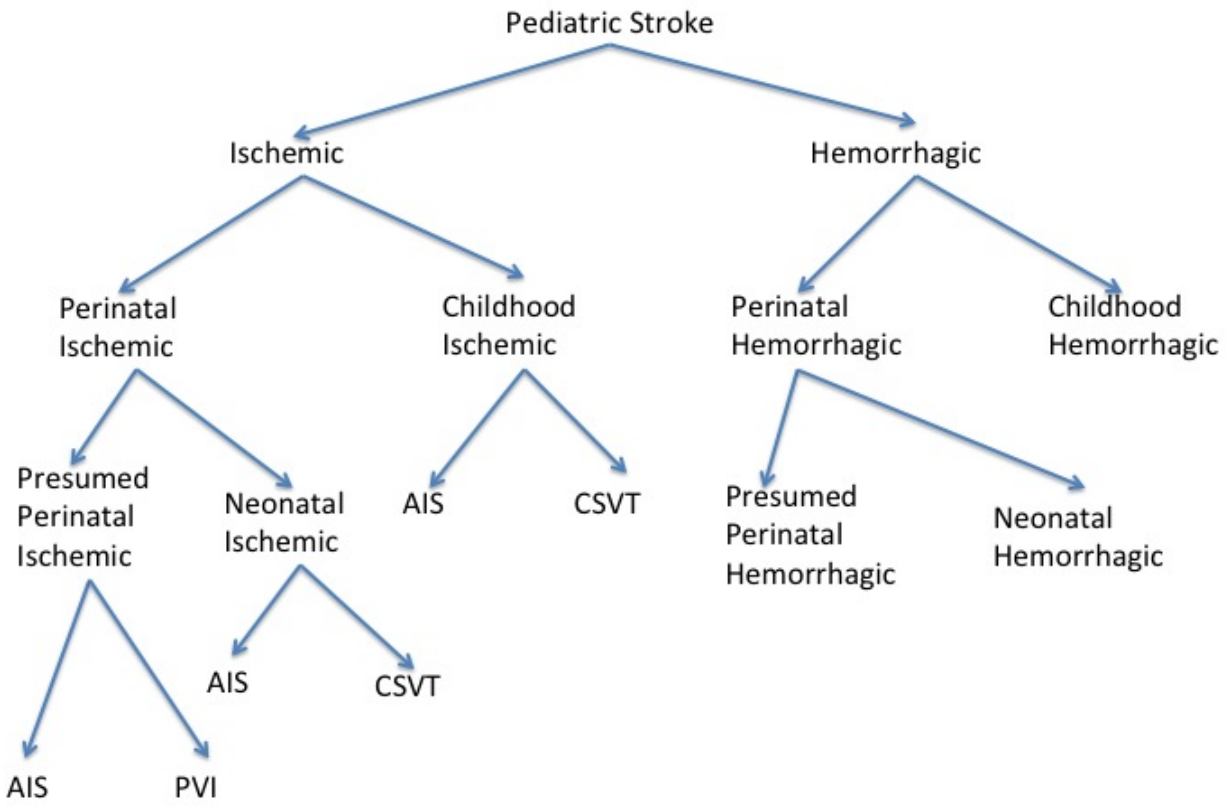
Classification of Pediatric Stroke

Depending upon the pathology involved, pediatric stroke may either be ischemic or hemorrhagic (Figure 1.1). Ischemic stroke is more frequently caused by arterial occlusion, but it may occur as a result of venous occlusion of cerebral veins or sinuses. Hemorrhagic stroke is

caused by bleeding from a ruptured cerebral artery or from bleeding into the site of an AIS. Ischemic stroke encompasses arterial ischemic stroke (AIS) and cerebral sinus venous thrombosis (CSVT), whereas hemorrhagic stroke includes intracerebral and subarachnoid haemorrhage (SAH).

Stroke occurs in children of all ages. Depending upon the age of onset, pediatric stroke can be divided into perinatal and childhood stroke. According to a recent consensus based classification system, perinatal stroke is defined as a vascular event causing focal interruption of blood supply, occurring between 22 weeks of fetal life through the 28th postnatal day and confirmed by neuroimaging (Raju et al., 2007; Lynch, 2009). Perinatal stroke is further sub-classified into neonatal and presumed perinatal stroke. Neonatal stroke has its onset from the time of birth to 28 days of age. A diagnosis of presumed perinatal stroke is made when an infant has, what appears to be a normal neonatal course, and usually presents in the first 18 months of life, often showing focal signs of hemiplegia. Post-perinatal neuroimaging reveals chronic changes suggestive of a vascular event involving one of the middle cerebral arteries, or the periventricular region during an earlier period. Given that there had been no historical event suggestive of a stroke during the childs' life, it is presumed to have occurred prior to birth. Perinatal stroke is responsible for 35-46% of all cases of pediatric ischemic stroke (Steinlen et al., 2005; Fullerton et al., 2007). Childhood stroke is described as a vascular event occurring between 28 days to 18 years of age resulting in irreversible focal damage to brain parenchyma, sudden onset of a neurologic deficit and confirmed by neuroimaging (Lynch et al., 2002). Both perinatal and childhood strokes can be of ischemic or hemorrhagic in origin. Childhood and neonatal ischemic strokes can be further subdivided into AIS and CSVT. Presumed perinatal stroke is further categorised as AIS or periventricular venous infarction (PVI) (Kirton et al., 2008; Takanashi et al., 2003; Takanashi et al., 2005). Fetal germinal matrix hemorrhage with parenchymal involvement leads to PVI in utero. The resulting compressive medullary venous infarction of the periventricular white matter presents as PVI.

Figure 1.1: Classification of Pediatric Stroke



Epidemiology of Pediatric Stroke

Stroke in infants and children occurs with a frequency of greater than 3.0/100,000; an incidence equal to that of childhood cancer (Lynch et al., 2002; Fullerton et al., 2003; deVeber et al., 2000a). A population-based study from France have reported an incidence up to 13/100,000 (Giroud et al., 1995). The incidence of pediatric stroke has increased in the last decade due to (1) advancements in neuroimaging techniques (2) improving health care and (3) better treatment of predisposing conditions such as congenital heart disease, sickle cell disease prematurity and tumours (Lynch et al., 2002; Lynch, 2004).

Incidence rates for ischemic stroke are estimated to be 0.2 to 7.9 (Satoh et al., 1991; Giroud et al., 1995). However, this is likely an underestimate, as the index of suspicion for ischemic stroke is typically low in the pediatric population, and data reporting these incidence

rates have been obtained through retrospective studies (Agarwal et al., 2009; Lyle et al., 2011). Further, there is lack of awareness about pediatric stroke often leading to under diagnosis and delay in diagnosis. Neurological presentation of pediatric stroke is also often subtle leasing to a diagnostic delay. Incidence rate for CSVT have been reported in only a few studies but the AIS is responsible for the large majority of ischemic strokes with CSVT forming a small proportion of ischemic strokes (Fullerton et al., 2003). The largest study of childhood CSVT reports an incidence rate of 0.67 per 100,000 (deVeber et al., 2001). The incident rate for haemorrhagic stroke ranges from 0.7 to 5.1 (Earley et al., 1998; Giroud et al., 1995). AIS accounts for about half of all strokes in children (Carvalho & Garg, 2002).

The incidence of perinatal stroke has been estimated at 1 in 1600 to 5000 births (Perlman et al., 1994; Estan & Hope, 1997; Wu et al., 2004; Schulzke et al., 2005; Lee et al., 2005; Laugesaar et al., 2007). Older studies on perinatal stroke had focused only on neonatal AIS patients (Perlman et al., 1994; Estan & Hope, 1997, Schulzke et al., 2005). The incidence rate of neonatal AIS in these studies ranges from 17.8 to 43.4 per 100,000 live births. However, more recent studies have included retrospectively diagnosed cases as well as hemorrhagic stroke. A population-based study of perinatal stroke in the USA that included both acutely and retrospectively diagnosed cases reported an overall incidence of 20 per 100,000 live births (Lee et al., 2005). A study in Estonia, which included acute, delayed, and hemorrhage cases found a much higher rate at 63 per 100,000 live births (Laugesaar et al., 2007). In both of these studies, the proportion of retrospectively diagnosed cases was higher than acute cases suggesting that the burden of perinatal stroke may be greater than that reported previously.

Morbidity of Pediatric Stroke

Stroke is also an important cause of childhood mortality and morbidity. Stroke ranks amongst the top ten causes of death in children and is associated with serious morbidity in children (Fullerton et al., 2003, Mallick & O'Callaghan, 2010). Further, the morbidity of neonatal and childhood stroke lasts a lifetime, amplifying the burden on children, families and society. The minimum annual cost of acute pediatric stroke in the United States is $42 million (Perkins et al., 2009). The economic burden of pediatric stroke is also sustained, with the five-year health care cost being 15 times that of age matched children, who have not suffered a stroke (Gardner et al., 2010).

Neurological deficits ranging from mild to severe, are witnessed in several aspects of life. These may include: sensorimotor deficits, cognitive impairments, behavioural issues, language expression and comprehension problems, visual impairment, hearing problems, developmental deficits, mental retardation, learning disabilities, movement disorders, headache, epilepsy, etc. Motor deficit is the most common disability observed after pediatric stroke. Children may have impairments in all areas, one or several areas.

Neurological impairments occur in 60-85% children, who have had a childhood AIS (Ganesan et al., 2000, Steinlin et al., 2004; Hartel et al., 2004; Hurvitz et al., 2004; Chabrier et al., 2000; deVeber et al., 2000b). In the largest published cohort study, authors reported neurological deficits in 74% of children at the time of hospital discharge (Goldenberg et al., 2009). This is similar to the observed rate of neurologic deficits in several studies with follow-up beyond 1 year.

Perinatal stroke is recognized as the leading cause of hemiplegic cerebral palsy in children (Kirton & de Veber, 2006; Lynch, 2009). Motor deficits are more common after presumed perinatal stroke, as hemiplegia is often the presenting symptom in this group. Motor deficits occur in up to 82-100% children presenting with presumed perinatal stroke (Curry et al., 2007; Lee et al., 2005; Wu et al., 2004; Laugesaar et al., 2007; Golomb et al., 2001). In contrast, motor disability is reported in 22-48% children with neonatal AIS (Curry et al., 2007; Lee et al., 2005; Boardman et al., 2005; Mercuri et al., 1999; Mercuri et al., 2005; Husson et al., 2010, Sreenan et al., 2000).

Quality of Life

The term "*quality of life*" (QOL) is used in our everyday life to describe the well-being of individuals and societies. WHO defines QOL as an "individual perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (Oort., 2005). In simple words, QOL can be defined as the degree of satisfaction or dissatisfaction felt by people with various aspects of their lives.

As the advances in diagnostic and therapeutic sciences have led to better cure rates, decreased mortality and improved survival in various chronic and life-threatening illnesses, the number of survivors with residual morbidity is exponentially increasing and a growing concern

is the QOL of the survivors (Eiser & Morse, 2001). The ultimate aim of health care is not just to increase the life expectancy but also to improve the QOL of the survivors.

Health Related Quality of Life

QOL incorporates all aspects of life and has been used in a variety of disciplines such as geography, philosophy, medical sciences, social sciences, health promotion, and advertising (Oort et al., 2005). It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment (Oort., 2005). Those aspects of QOL that are related to the health of an individual is described as health related QOL (HRQL) (Ferrans et al., 2005). HRQL takes into account value or importance assigned to a health status by the patient.

HRQL is a multidimensional construct encompassing all 3 domains of health: physical, mental and social that provides patient's assessment of their physical, mental and social well-being (Bradley & Tamburini, 2003, Bullinger, 2003; Ferrans et al., 2005). HRQL assessments provide a comprehensive picture of patient health status as it captures both objective and subjective aspects of health. The objective component refers to the functioning concept i.e., what the person can do. It includes domains like physical functioning (limitations in physical activities e.g., walking), social functioning (effect of physical and emotional health on normal social activities), role physical (problems with work or daily activities as a result of physical health) and role emotional (problems with work or daily activities as a result of emotional problems). The subjective component pertains to the well-being concept i.e., how the person feels. The domains covered are emotional well-being (happiness, nervousness, depression), pain (limitations in any activity due to pain) and vitality (energy and tiredness).

Traditional outcome measures of morbidity and mortality are objective and often limited in their potential to achieve a comprehensive assessment of the health status of an individual inclusive of their physical, mental and social well-being. In this regard, HRQL tools have a promising and adjuvant role since they evaluate the health across multiple domains i.e., physical, mental and social, a concept that conform to the WHO definition of health (Morris et al., 2009; Bradley & Tamburini, 2003). WHO defines health as a state of physical, mental and social well-

being and not merely the absence of disease or infirmity (International Health Conference, 1946). Hence, owing to the broad assessment provided by these tools, HRQL is increasingly being recognized as a key outcome indicator in chronic diseases such as stroke (Ingerski et al., 2010; Haley et al., 2011; Kissela, 2006). More importantly, HRQL instruments are self-report measures that measure patient own perception about the impact of disease or treatment on health, well-being and daily living, thereby, making the HRQL concept more relevant to affected patients and their families. In fact, self-assessed health status has been proved to be more powerful predictor of mortality and morbidity than many objective measures of health (Dominick et al., 2002; DeSalvo et al., 2006).

Applications of HRQL Research

HRQL is being increasingly accepted as an important outcome measure in health care and delivery (Greenfield & Nelson, 1992; Wilson & Cleary, 1995; Varni et al., 2005; Varni et al., 2006). Being a patient-based subjective measure, the concept of HRQL has gained increased popularity over the last few decades. These patient-reported outcome measures are acknowledged as vital instruments for evaluation of health care needs of a community, resource allocation, planning and health policy making, and prioritization of health care and social support services (Marshall et al., 2006). Further, these tools have an indispensible role to play in the evaluation of health care services, measurement of intervention outcomes and comparison of treatment costs and benefits. These measures are also of potential value in comparing outcomes in clinical trials and to assess the outcomes of new treatments. Assessment of HRQL is also important during provision of palliative care (Eiser & Morse, 2001).

Measuring HRQL has other associated benefits. HRQL assessment also helps determine the burden of a disease and resulting disabilities. HRQL data helps identify the subgroups with relatively poor perceived health and can provide valuable insight into designing interventions needed to improve their situations and avert more serious consequences. A better understanding of the relationships between HRQL and its determinants and risk factors can guide the development of measures focused towards prevention of those risk factors and enhancement of HRQL.

HRQL research has numerous other applications. The incorporation of standardized HRQL measures in routine clinical care has been demonstrated to improve the patient-provider communication and clinical management (Velikova et al., 2004; de Wit et al., 2008). It has also shown to improve the patients' emotional well-being and satisfaction. Further, health status and HRQL measures are also commonly used for health surveys and health evaluation of the general population. And similar to the patient population, the data gathered serve multiple purposes including well-being of the general population, perceived health problems, regional comparisons of health, assessment of health care needs, planning and policy making and assessment of determinants of health.

The study of HRQL in the general population has also led to the introduction of a new concept in population health: Health adjusted Life Expectancy (HALE) (Public Health Agency of Canada, 2012). HALE is defined as the life expectancy weighted for the level of HRQL. In other words, HALE is defined as the average number of years in a healthy state that an individual can expect to live. It is a summary measure that provides a single indicator of population health by taking into account both morbidity and mortality. It can be used to measure the burden of disease and injury in the population, risk factors and the performance of public health efforts. Thus, measuring HRQL also helps tracking a nation's progress in achieving population health goals (Centers for Disease Control and Prevention, 2011).

HRQL Assessment

HRQL is measured using specific tools or instruments. There are 2 set of tools available: generic or disease specific (Andresen & Meyers, 2000; Wells et al., 2011). Generic measures are applicable to any patient regardless of the prevailing medical condition whereas disease specific tools target a specific disease population. Generic HRQL measures encompass broader health domains such as physical, emotional, social, and role functioning and enable comparisons across patient populations. Although easy to apply, the generic measures tend to miss some subtle and crucial aspects because of being non-disease specific. Disease specific scales contain condition-specific symptoms and take a patient centered approach to item development. These measures may achieve improved measurement sensitivity for health domains relevant to a disease or condition. Additionally, disease specific instruments tend to be more responsive and are essential

for longitudinal studies designed to evaluate changes in HRQL over time and to judge the impact of health improving interventions.

Generic HRQL measures can be further classified into 2 broad categories: Profile measures and Utility measures. Profile measures yield a profile of health outcomes. The most frequently used profile HRQL measure is the 36-Item Short Form Health Survey (SF-36) (McDowell & Newell, 1996). The SF-36 includes 8 health concepts: physical activity, role–physical, bodily pain, general health perceptions, vitality, social functioning, role–emotional, and mental health and generates 8 profile scores and 2 summary scores. Since profile measures provide scores across various dimensions, they are very vital in determining the impact of disease on each subscale and in assessing the differential effect of the interventions. The most commonly used profile measure in children is the PedsQL.

The utility measures (e.g., Health Utility Index 2 and 3, EuroOoL) are also comprehensive and permit broad comparisons like profile measures. In addition, these HRQL tools generate preference based scores based on the value that the patient attaches on a subjective health state (Feeny, 2000). Further, these tools generate a single summary score of the outcome where full health is scored one and zero is equivalent to death. Thus, it takes into account both, morbidity and mortality. A single overall outcome score is also more convenient for statistical comparisons and to judge the effect of any intervention as it shows the net effect achieved. In addition, these are essential tools for calculation of Quality Adjusted Life Years (QALYs) and are vital for economic evaluation as cost effective analysis can be performed to know the economic impact of strategies targeted towards enhancement of the HRQL (Feeny et al., 1996)

HRQL in Children

HRQL in children differs from adults in some aspects. In children, the concept of HRQL further expands to involve family, friends, school and environment in addition to physical, social and emotional domains of health. And, since a child's and family's QOL are interconnected, a child's QOL is dependent on others in her/his life. Thus, HRQL in children arises from a dynamic relationship among all elements. There are developmental considerations as well as the concept of HRQL changes over time. This makes assessment of the HRQL much more difficult in a pediatric population than adult.

Unlike the majority of adults, where self-report is the standard method for assessment of HRQL, parent proxy assessment of HRQL is much more commonly employed in children since young children especially under 5 years are not cognitively mature enough to report their own HRQL. However, the parent reports may not be able to provide an accurate judgement of their children's HRQL due to the lack of concordance between self and proxy reports (Varni et al., 1999). It is still important to have both self and proxy assessment as this may provide a comprehensive picture of children HRQL. These may provide different, but important, perspectives that can influence health care. Mode of administration is also important in pediatrics as the children between 5-7 years might not be able to read the questions themselves but can answer correctly when same questions are read to them. HRQL tools in children are also limited, valid over a narrow age range (many are not applicable to infants and small children), and have not been extensively validated as in adults. The utility measures are also still under employed in pediatric research.

HRQL Assessment in Pediatric Population

In pediatrics, there are an array of measures of HRQL including Pediatric Quality of Life Inventory (PedsQL), Child Health Questionnaire (CHQ), Child Health and Illness Profile (CHIP), HRQL in Children and Adolescents (KINDL-R), TACQOL and HRQL in Children and Adolescents (KIDSCREEN). These differ considerably in terms of their health concepts, domains, items, scoring and valid age range so a direct comparison of these measures is not feasible. Stroke specific HRQL scale has already been developed and validated in adults since 1999 (Williams et al., 1999). However, no stroke specific scale exists in children.

The PedsQL (© 1998-2012 James W. Varni, Ph.D. All rights reserved) is the most widely used generic HRQL measure in children. The instrument has both self and proxy report versions and is applicable over a wide age range of 2-18 years. There are four surveys for different age categories: Toddler (ages 2-4), Young Child (ages 5-7), Child (ages 8-12), and Teen (ages 13-18). Only proxy report is available for toddler age group. Both self and proxy report versions are available for other age groups (Varni et al., 2003).

The instrument has 23 items encompassing 4 areas of functioning: physical, emotional, social and school. The survey takes approximately 10 minutes, and respondents are asked to rate

how much each item has been a problem in the past month. Users respond on a Likert scale from 0-4 (0 = never; 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always), with the exception of the self-report Young Child survey, which is simplified into a 3-point Likert scale (0 = never; 2 = sometimes; 4 = almost always). The self-report Young Child survey is further simplified, by showing different faces to correspond to the ratings (smiling face = never; neutral face = sometimes; frowning face = almost always) (Varni et al., 2001). Items are reverse scored and linearly transformed to a 0-100 scale (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0), with higher converted scores indicating better HRQL. The instrument provides four domain scores, two summary scores (physical and psychosocial functioning) and a total HRQL score. US population norms are available for comparison.

The PedsQL has adequate psychometric properties with internal consistency ranging from 0.70 to 0.89 for proxy-report and 0.54 to 0.86 for self-report (Varni et al., 2001). Construct validity of the PedsQL has been demonstrated in several populations by its ability to accurately differentiate HRQL between typically developing children and children with chronic or acute health conditions (Varni et al., 2001).

HRQL in Pediatric Stroke Survivors

The morbidity after pediatric stroke affects several aspects of life and lasts a lifetime influencing the daily life, and potentially influencing the overall well-being and HRQL of survivors. The magnitude of long term neurological and cognitive deficits, and functional disabilities after pediatric stroke has been objectively assessed in several studies (Ganesan et al., 2000; Golomb, 2009; Steinlin et al., 2004; Hartel., 2004). To attain an objective evaluation of the long term outcome of pediatric stroke, scales including pediatric stroke outcome measure (PSOM) have also been developed and validated (deVeber et al., 2000b). However, PSOM is an objective measure completed by the clinicians and not a patient reported outcome measure. The objective parameters of the physical and functional status are limited in their potential to achieve a comprehensive assessment of the health status of an individual.

Evaluation of HRQL in survivors of pediatric stroke is essential to understand the impact of residual morbidities on daily living and well-being. It is also important to learn the effect of pediatric stroke on different domains of HRQL to know what domains are affected the most so

that targeted interventions can be developed. HRQL assessment of pediatric stroke patients can provide a comprehensive and subjective assessment of well-being to guide the development of appropriate health improving interventions. Both self and proxy assessment and their correlation of HRQL is also important in pediatric stroke patients as they are often limited in their view point due to immaturity and underlying cognitive deficiencies.

Literature on the HRQL of pediatric stroke survivors is limited and the available literature has methodological limitations. To date, HRQL in survivors of pediatric stroke has been reported in a few studies (O'Keeffe et al., 2012; Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg., 2010; Everts et al., 2008; Simma et al., 2007; Friefeld et al., 2004; Han et al., 2004; Gordon et al., 2002). Most of these studies have emerged from Europe and report a small sample size. In addition, HRQL after perinatal stroke is underreported. Further, these studies are limited in their methodology and interpretation of the HRQL data, which should be assessed for both statistical significance and clinical importance. It is vital to have a clear and thorough reporting of HRQL data since patient reported outcome is the only measure of assessing patient's perspective.

Literature reports lower HRQL in pediatric stroke population in comparison to the reference population. A direct comparison of studies addressing HRQL in survivors of pediatric stroke is difficult because of the clinical heterogeneity of the patient population involved and the variety of measures being used for assessment. In a study from Sweden, authors evaluated HRQL of 17 children and 19 young adults (age range: 5.5-26.1 years) with pediatric stroke, by using the child health questionnaire (CHQ) and short form health survey (SF-36), respectively (Christerson & Stromberg, 2010). The authors reported significantly reduced scores in the stroke cohort compared to normative data. Parent proxy reports showed lower mean scores for children in several domains including physical, social and emotional. In contrast, children indicated significantly reduced scores in only physical health items. Young adults did not show a significant difference in any dimension of HRQOL compared to healthy controls. In a study from the Netherlands, authors assessed HRQL in 66 children (age range: 1-15 years) with childhood arterial ischemic stroke using age specific generic questionnaires (Cnossen et al., 2010). The results derived from parent proxy reports were similar to Swedish population but, on the contrary, children reported more social problems. In contrast, authors from Austria have

demonstrated a good QOL in 16 out of 20 children with stroke (age range: 1-14 years) using the parent form of CHQ (Simma et al., 2010).

Studies of HRQL in pediatric stroke survivors have reported variable findings with respect to the domains affected. Physical function has been observed to be most significantly impaired in two studies (Gordon et al., 2002; Han et al., 2004) whereas school functioning is reported to be more problematic in another (Friefeld et al., 2010). In a Canadian study, authors evaluated HRQL of 84 arterial ischemic stroke and 16 cerebral sinus venous thrombosis children using the PedsQL (Friefeld et al., 2004). The authors reported lower HRQL in all domains including physical, emotional, social and school in both self and proxy report forms. However, the school domain was rated to be the most poor by parents. This difference between various studies with respect to the domains reported most problematic may be attributed to the differences in parent perception, cultural differences, and heterogeneity of patient population.

There is little information available on risk factors associated with poor HRQL after pediatric stroke, making it difficult to implement important strategies to improve outcome. Only neurological deficits have demonstrated a consistent relationship with poor HRQL but it accounts for only a small variance in HRQL (Neuner et al., 2011, Cnossen et al., 2010; Simma et al., 2007; Friefeld et al., 2004). Friefield et al. examined the influence of socioeconomic status (SES), gender and neurological outcome on HRQL in 99 children with ischemic stroke and found only female sex and neurological deficits as significant predictors of poor HRQL (Friefeld et al., 2004). In adult literature, determinants of HRQL after stroke have included ethnicity, SES, right hemispheric lesions and underlying heart disease (Patel et al., 2007). To ensure a better understanding of HRQL and develop future strategies, a detailed systematic evaluation of factors affecting HRQL at child, family and community level is warranted. A better understanding of the relationships between HRQL and its determinants may help identify the subgroups with relatively poor perceived health and can provide valuable insight into designing interventions needed to improve their situations and avert more serious consequences. Hence, this study was designed to systemically evaluate the HRQL and its determinants in a pediatric ischemic stroke population.

Research Questions

1. Is HRQL in pediatric ischemic stroke patients different compared to a healthy population?
2. What domains of HRQL are affected in survivors of pediatric ischemic stroke?
3. What factors influence HRQL in pediatric ischemic stroke survivors?
4. What is the agreement between self and proxy reports in assessment of HRQL in a pediatric stroke population?

Research Hypothesis:

1. HRQL of pediatric ischemic stroke patients is lower compared to a healthy population.
2. HRQL is impaired across multiple domains of health in survivors of pediatric stroke.
3. There are several variables at the child and family level including neurological outcome, age of onset of stroke, socioeconomic status that influence HRQL across health domains.
4. The degree of agreement between self and proxy reports is fair to good.

Chapter Two: Health Related Quality of Life of Pediatric Ischemic Stroke Survivors - A detailed assessment using parameters of clinical importance

With the extensive developments in diagnostic and therapeutic fields, pediatric stroke is increasingly recognized. The incidence of pediatric stroke has risen to >3.0/100,000; equal to that of childhood cancer (Lynch et al., 2002; Fullerton et al., 2003). Stroke ranks amongst the top ten causes of death in children and is the leading cause of hemiplegic cerebral palsy (Fullerton et al., 2003, Kirton & deVeber, 2006). Neurological deficits, ranging from mild to severe, in motor, cognition, language and behaviour spheres are observed in 70-75% of survivors of pediatric stroke and influence the overall well-being of children and their families (Ganesan et al., 2000; Golomb, 2009; Steinlin et al., 2004; Hartel., 2004). Further, the morbidity of neonatal and childhood stroke lasts a lifetime, amplifying the burden on children, families and society.

The magnitude of long-term neurological and cognitive deficits, and functional disabilities after pediatric stroke has been objectively assessed in several studies (Ganesan et al., 2000; Golomb, 2009; Steinlin et al., 2004; Hartel., 2004). However, objective parameters of the physical and functional status are limited in their potential to achieve a comprehensive assessment of the health status of an individual inclusive of their physical, mental and social well-being. In this regard, HRQL tools have a promising and adjuvant role since they evaluate the health across multiple domains i.e., physical, mental and social, a concept that conform to the WHO definition of health (Morris et al., 2009). Hence, owing to the comprehensive assessment provided by these tools, HRQL is increasingly being recognized as a key outcome indicator in chronic diseases such as stroke (Ingerski et al., 2010). More importantly, HRQL instruments are self-report measures that measure patient own perception about the impact of disease on health, well-being and daily living. In fact, self-assessed health status has been proved to be more powerful predictor of mortality and morbidity than many objective measures of health (Dominick et al., 2002; DeSalvo et al., 2006). Further, these patient-reported outcome measures are also acknowledged as vital instruments for evaluation of health care needs of a community, resource allocation, planning and health policy making, and prioritization of health care and social support services (Marshall et al., 2006).

Evaluation of HRQL in the pediatric stroke population is essential to achieve a comprehensive and subjective assessment of well-being to guide the development of appropriate

health improving interventions. To date, HRQL in survivors of pediatric stroke has been reported in some studies (O'Keeffe et al., 2012; Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg 2010; Everts et al., 2008; Simma et al., 2007; Friefeld et al., 2004; Han et al., 2004; Gordon et al., 2002). Most of these studies have emerged from Europe and report a small sample size. These studies often report a heterogeneous patient population encompassing different kinds of stroke. Further, the studies are limited in their methodology and interpretation of the HRQL data, which should be assessed for both statistical significance and clinical importance. A clear and thorough reporting of such data is imperative since patient-reported outcome is the only measure of assessing a patient's perspective. Also, there is little information available regarding factors predict HRQL after pediatric stroke, making it difficult to implement important strategies to improve outcome (Neuner et al., 2011; Cnossen et al., 2010; Friefeld et al., 2011). A better understanding on the relationship between HRQL and its determinants may help identify the subgroups with relatively poor perceived health and can provide valuable insight into designing interventions needed to improve their situations and avert more serious consequences. Hence, this study was designed to provide a detailed assessment of HRQL and its determinants in survivors of pediatric ischemic stroke using measures recommended for interpretation and reporting of the patient-reported outcome data (Revicki et al., 2007).

Methodology

Study population:

A cross-sectional study was conducted at the Stollery Children's Hospital, Edmonton, Alberta, Canada, a tertiary care pediatric hospital catering to and receiving referrals from a major region in Western Canada (whole of Northern Alberta, parts of Saskatchewan and Manitoba). Children diagnosed with pediatric ischemic stroke between January 2003 and June 2012 were identified through a pediatric stroke database and considered for participation if: (1) the child was age 2-18 years at assessment; and (2) at least 1-year follow-up had occurred after childhood stroke. The diagnosis of ischemic stroke was confirmed on MRI or CT scan in all patients at the time of initial presenation. A cut-off age of 2 years was selected as HRQL is difficult to evaluate in very young infants, and there are very few HRQL tools available for infants and small children. A minimum of 1-year of follow-up was decided for childhood stroke patients to allow the peak period of neurological recovery to occur following the onset of stroke so as to have a

fair assessment of the long-term outcome and HRQL after pediatric stroke. For this study, children with global brain injury, watershed infarcts, intracranial hemorrhage, cerebral sinovenous thrombosis, transient ischemic attacks, underlying genetic syndromes, or other associated brain pathologies or neurological comorbidity e.g., autism etc. were excluded. The study was approved by the Health Research Ethics Board at the hospital.

After obtaining an informed consent, the caregivers of all eligible children were recruited either during our routine pediatric stroke clinics or over the telephone. All study participants were provided with, or mailed a set of standardized questionnaires. To ensure a uniform assessment and prevent any bias related to the mode of administration, all participants were given a paper copy of the survey, advised to complete it at home and mail it back.

Neurological outcome assessment:

Neurological outcome and need of on-going rehabilitative health care services was assessed at the same time HRQL assessment was performed by using the Pediatric Stroke Recurrence and Recovery Questionnaire (RRQ). The RRQ is a standardized measure adapted from the Pediatric Stroke Outcome Measure (PSOM) to assess the post-stroke neurological function and recovery from pediatric stroke. It is completed by the parents and has been recently validated (Lo et al., 2012). The RRQ measures the type and degree of neurological impairment across 5 categories: right sensorimotor, left sensorimotor, cognition/behavior, language production, and language comprehension. The neurological deficits in each category are scored as 0 (no neurological deficit with no loss of function), 0.5 (mild deficit, normal function), 1 (moderate deficit with decreased function) or 2 (severe deficit with complete absence of function). In addition, global neurological outcome is also reported either as a linear variable (overall RRQ score) or a dichotomous variable (with an outcome of good or poor). The Overall RRQ score ranges from 0 to 10, with 0 being no impairment and 10 being maximum level of impairment (score 2) in all 5 domains. Good outcome encompasses children with normal (0 score in all 5 categories) and mild deficit (0.5 score in only 1 category). Poor outcome refers to children with a moderate deficit (score of 0.5 in 2, 3, or 4 categories; or 1 in 1 category; or 1 in 1 category plus 0.5 in 1 category) or a severe deficit (score of 0.5 in all 5 categories; or 1 in 2 categories; or 1 in 1 category plus 0.5 in 2 categories; or 2 in 1 category) (Neuner et al., 2011).

HRQL assessment:

HRQL was evaluated using proxy report versions of the Pediatric Quality of Life Inventory (PedsQL4.0) and compared to the US population norms (Varni et al., 2003). The PedsQL is the most widely used generic HRQL measure in children applicable over an age range of 2-18 years and has adequate psychometric properties of reliability and validity (Varni et al., 2003). The instrument has 23 items encompassing 4 areas of functioning: physical, emotional, social and school and a recall period of 1 week. Participants respond on a Likert scale from 0-4. Items are reverse scored and linearly transformed to a 0-100 scale with higher converted scores indicating better HRQL. The instrument provides four domain scores, two summary scores (physical and psychosocial functioning) and a total HRQL score.

Socio-demographic, clinical and radiological data:

Medical records of all study participants were reviewed to obtain data on demographic, clinical (age of presentation, side and clinical signs at presentation), and neuroimaging characteristics. All neuroimaging, performed as a part of routine clinical practice on all patients, consisted of sagittal T1-weighted, axial T2-weighted, diffusion weighted and fluid attenuated inversion recovery imaging and were reported by a radiologist and independently reviewed by a pediatric neurologist (JYY). The first MRI obtained after the clinical suspicion of stroke was used to determine the radiological parameters (vascular territory involved, size, site and lateralization of stroke). Vascular territories were defined using the published resources (Kirton et al., 2008). Size was determined as an infarct involving less than <1/3, 1/3-2/3 and >2/3 of the ipsilateral cerebral hemisphere. All relevant details were extracted using a pre-designed standardized proforma. Children were categorized as presumed perinatal, neonatal or childhood stroke, based on neuroimaging and historical features by a pediatric neurologist who specialized in stroke. Socioeconomic status was determined using the four factor index of social status through the information obtained via a parental questionnaire on parents' education, occupation and marital status (Hollingshead, 1975). Information on residence, ethnicity, any comorbidity and total number of children in the family were also obtained through a parental questionnaire.

Statistical analysis:

Statistical analysis was performed using the STATA version12. A priori sample size calculation revealed a required sample size of 75 to detect an effect size of 0.25 with a study power of 80 and α of 0.05. Categorical and continuous variables were expressed as proportions and means/medians, respectively. HRQL data were interpreted for statistical significance by comparing the HRQL scores with published US norms using unpaired student t-test. HRQL data were also assessed for clinical importance using 2 different approaches: (i) norm based, and (ii) anchor based (Revicki et al., 2007). The norm based strategy involved comparing the data to a normal distribution, which is characterized by a standardized score such as Z-score. Z scores were computed as difference between the patient sample mean and reference mean, divided by the standard deviation of the reference population. Population norms from US were used as the reference population (Varni et al., 2003). Effect sizes to assess the magnitude of difference in HRQL scores were also computed using the same formula as Z-score. These were interpreted as small (0.20 to 0.49), moderate (0.50-0.79) and large (>0.80) based on Cohen's recommendations (Cohen., 1988). In literature on HRQL, a difference of one half a standard deviation (0.5 SD) or moderate effect size has been suggested as a minimally important difference (Norman et al., 2003). Thus, a Z-score of 0.5 or moderate effect size would have indicated a clinically important difference in our patient population.

The anchor based interpretation involved the comparison of scale scores with some external anchor. In our study, neurological outcome as assessed by RRQ was used as an external anchor. Further, the absolute difference in HRQL scores was also compared with the minimal clinically important difference (MCID) published in the literature (Varni et al., 2003). MCID is defined as the smallest difference in the HRQL measure that is perceived to be clinically important in a population. The MCID for PedsQL has been generated from the Standard Error of Measurement (Varni et al., 2003).

A univariate linear regression analysis was performed to identify HRQL predictors and results were expressed as mean difference in scores with 95% confidence intervals (CI). A negative value indicated that the predictor was associated with worse QOL, whereas a positive difference suggested the predictor was associated with better QOL. A multiple regression analysis was also conducted to identify independent predictors of the HRQL. Variables were selected for a multivariate analysis based on their clinical importance and statistical significance

($p<0.10$). Vascular territory was not included due to sample size limitations. All tests of significance were two-sided and statistical significance was defined as $p<0.05$.

Results

Ninety pediatric ischemic stroke patients were enrolled. Table 2.1 provides the baseline demographic information of all 90 patients. The male to female ratio was 1.3 (51 males, 39 females) and mean age at diagnosis of stroke was 17.3 months (range: neonate to 168.5 months). The age distribution was as follows: Neonatal (40%, n=36), presumed perinatal (34%, n=31) and childhood (26%, n=23). The mean age at assessment was 6.4 (range: 2.1-17.9) years. When divided by age group, 58 (64%) children were 2-5 years and 32 (35.6%) were >5 years of age. Patients were followed up on an average for 5.1 years (range 1-15.2 years) after the onset of stroke. About a quarter (28%) of these patients had normal global outcome, whereas 62% had deficits ranging from moderate to severe (Table 2.2). Motor outcome was normal in only one-third of patients (34%) with residual impairments in 66% patients. Impairments in cognition, behaviour and language domains were slightly less evident than motor impairments. Around half (44%) of the patients were still not independent in their day-to-day activities and more than one-third (41%) were receiving some form of rehabilitation therapy at the time of follow-up.

Table 2.3 presents the proxy reported HRQL scores of all 90 patients. These include PedsQL overall, physical and psychosocial summary scores as well as the emotional, social and school domain scores of the psychosocial dimension. Since some children did not attend school, 72 responses were available for the school dimension. These assessments were completed by mother in the majority of children (n=82). A father, foster mother or step-mother provided assessments in 5, 2 and 1 children, respectively. In comparison to the reference population, a statistically significant difference was demonstrated in all domains except the school functioning domain. Z scores were negative in all domains indicating the lower HRQL in the patient population compared to reference population. These were in the clinically important range for all except the school functioning domain. Effect sizes also indicated a clinically important difference in all except the school functioning domain. The absolute difference in the HRQL scores of patient and reference population also exceeded the MCID published in the literature in all except the school functioning domain. Z-scores were most negative in the emotional functioning domain suggesting maximum impairment in the emotional domain.

When assessed in relation to an external anchor i.e., neurological outcome as measured by the RRQ, HRQL was found to significantly vary by the degree of impairment. An inverse linear relationship was documented between the two. For instance, for every one unit increase in the RRQ score, there was a 7.2 unit decrease in the total HRQL score ($p<0.001$) (Figure 2.1). Table 2.4 represents the comparison of HRQL scores across different domains with neurological outcome in different categories. Parents perceived significantly lower overall HRQL in children with moderate to severe global deficits. Children with overall mild deficits had a comparable HRQL to children with normal outcome. Across all other domains, HRQL was significantly lower across all level of impairments in relation to the corresponding neurological outcome categories. For instance, physical HRQL was significantly inferior across all motor outcome categories.

A multitude of clinical, sociodemographic and radiological variables were found to be predictive of overall HRQL by univariate linear regression analysis (Table 2.5). In the multiple regression analysis, neurological outcome, socioeconomic status, and site of stroke were found to be independently associated with overall HRQL. These 3 variables explained 50% variance in the total HRQL score. We found that those with poor neurological outcome had worse HRQL after pediatric stroke. Lower socioeconomic status was also associated with worse overall HRQL.

Discussion

HRQL studies are often limited in their interpretation and reporting of the quality of life data (O'Keeffe et al., 2012; Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg 2010; Everts et al., 2008; Simma et al., 2007; Friefeld et al., 2004; Han et al., 2004; Gordon et al., 2002). It is vital to have a clear and thorough reporting of such data since patient-reported outcome is the only tool to measure the patient's viewpoint. Interpretation of the HRQL data for clinically significant findings is also imperative to appropriately guide the health improving interventions. Specific guidelines do exist in the literature to aid the interpretation and presentation of such data (Revicki et al., 2007). In this study, we used these guidelines to assess the HRQL of pediatric stroke population. Our assessment included detailed reporting of the study population with clear inclusion and exclusion criteria. We also included clinical outcome as an external anchor and provided detailed information on instruments used, data collection

procedures, methods of analysis and methods of interpretation. Further, HRQL data were analysed using different approaches recommended for the interpretation and reporting of the patient reported outcome data.

Our study data analysed using different techniques yielded comparable results. Parents reported lower overall HRQL in their children compared to normative data. Results were in the statistically significant and clinically important range for all except the school functioning domain. Since the majority of our children were under 5 years of age, school functioning was not rated a major issue by parents. However, when children under 5 were eliminated from the analysis, school functioning also became an important domain.

Our study results indicated a lower HRQL in children with stroke compared to the reference population, which is consistent with some previous reports (O'Keeffe et al., 2012; Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg 2010; Everts et al., 2008; Simma et al., 2007; Friefeld et al., 2004; Han et al., 2004; Gordon et al., 2002). In contrast, authors from Austria demonstrated a good QOL in 16 out of 20 children (age range: 1-14 years) using the parent form of CHQ (Simma et al., 2007). A direct comparison of studies addressing HRQL in survivors of pediatric stroke is difficult because of the clinical heterogeneity of the patient population involved and the variety of measures being used for assessment. In a study from Sweden, authors evaluated HRQL of 17 children and 19 young adults (age range: 5.5-26.1 years) with pediatric stroke, by using the child health questionnaire (CHQ) and short form health survey (SF-36), respectively (Christerson & Stromberg 2010). The authors reported significantly reduced scores in their stroke cohort compared to normative data in several domains including physical, social and emotional. In a study from the Netherlands, authors assessed HRQL in 66 children (age range: 1-15 years) with childhood arterial ischemic stroke using age specific generic questionnaires and reported results similar to the Swedish general population (Cnossen et al., 2010).

Studies on HRQL of pediatric stroke survivors have reported variable findings with respect to the domains affected. Physical function has been observed to be most significantly impaired in some studies (Han et al., 2004; Gordon et al., 2002), whereas school functioning is reported to be more problematic in others (Friefeld et al., 2004). In the current study, parents perceived the maximum impairment and lowest HRQL in the emotional functioning domain for

their children. In another Canadian study, authors evaluated HRQL of 84 arterial ischemic stroke and 16 cerebral sinus venous thrombosis children using PedsQL (Friefeld et al., 2004). The study reported lower HRQL in all domains including physical, emotional, social and school. However, school domain was rated to be the most poor by parents. This difference between various studies with respect to the domains reported most problematic may be attributed to the differences in parent perception, cultural differences and heterogeneity of patient population.

Although a lower physical HRQL was also reported, the emotional functioning was rated to be the most affected domain by parents in our study. This is contrary to what is identified by physicians, who report the maximum deficits in the sensorimotor domain of pediatric stroke patients (Ganesan et al., 2000; Golomb, 2009; Steinlin et al., 2004; Hartel., 2004). These results emphasize the importance of having a comprehensive and quality of life assessment of these patients since HRQL assessment reveals what is more meaningful to patients and parents than usual clinical signs and symptoms perceived by clinicians. Health care providers need to understand not only the physical, but also the emotional and social aspects of pediatric stroke. These findings also necessitate the need to develop psychosocial interventions aimed at improving emotional and social functioning and self-esteem of pediatric stroke patients.

When assessed in relation to the neurological outcome, HRQL varied in inverse proportion to the degree of impairment. Although these results seem clinically intuitive, we demonstrated the magnitude of such associations, which is important for health care and delivery. A lower total HRQL was demonstrated in children with moderate to severe global deficits. No significant difference was exhibited in the total HRQL of children with mild global deficits compared to children with normal outcome. However, HRQL in individual domains was significantly impaired in children with even mild deficits in corresponding neurological outcome categories.

Our second objective was to describe predictors of poor HRQL after pediatric ischemic stroke. Little previous work has focused on identifying children who have poor HRQL after stroke. We found that children with poor clinical outcome and low socioeconomic status had worse HRQL. However, gender was not found to be predictive of HRQL in the current study, contrary to previous findings (Friefeld et al., 2004). Patients with neonatal onset of stroke demonstrated better HRQL than childhood stroke and presumed perinatal stroke patients.

However, age of stroke onset was not found to be predictive of total HRQL on multivariate analysis.

Table 2.1: Demographic parameters of participants (N=90)

Parameter	**Mean±SD (Range)**	**Median (IQR)**
Age at onset of stroke (months)	17.3±41.3 (0-168.5)	0 (0-2.5)
Age at assessment (years)	6.4 ±4.5 (2.1-17.9)	4.4 (3.1-8.7)
Time elapsed since stroke (years)	5.1±3.1 (1.0-15.2)	4.1 (2.8-6.6)

SD: standard deviation; IQR: interquartile range

Table 2.2: Neurological outcome of pediatric ischemic stroke survivors

Clinical Outcome	**Pediatric Stroke (n=90)**
Global outcome • Normal • Mild deficit • Moderate deficit • Severe deficit	 27.7 % (25) 10% (9) 26.7% (24) 35.6% (32)
Motor outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 34.4% (31) 15.6% (14) 33.3% (30) 16.7% (15)
Cognition and Behaviour outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 62.2% (56) 20% (18) 16.7% (15) 1.1% (1)
Language Production • No impairment • Mild impairment • Moderate impairment • Severe impairment	 57.8% (52) 18.9% (17) 18.9% (17) 4.4% (4)
Language Comprehension • No impairment • Mild impairment • Moderate impairment • Severe impairment	 74.4% (67) 14.4% (13) 7.8% (7) 3.3% (3)
Independence	55.6% (50)
Seizures at follow-up requiring AEDs	11.1% (10)
Ongoing Rehabilitation • Physical therapy • Occupational therapy • Speech therapy • Special education services	 41.1% (37) 41.1% (37) 23.3% (21) 17.8% (16)

AEDs: antiepileptic drugs

Table 2.3: Proxy assessment of HRQL of pediatric ischemic stroke survivors compared to reference population

HRQL domain	Mean score	SD	p-value	Z-score	Effect size	Absolute Difference	MCID*
Total score	72.58	19.14	<0.0001	-0.55	M	8.76	4.50
Physical Health	73.72	25.12	0.0005	-0.48	S-M	9.54	6.92
Psychosocial Health	72.31	17.94	<0.0001	-0.50	M	7.91	5.49
Emotional Functioning	69.83	21.25	<0.0001	-0.62	M	10.45	7.79
Social Functioning	74.02	19.81	0.0001	-0.4	S-M	8.13	8.98
School Functioning	72.71	21.61	0.08	-0.21	S	4.2	9.67

SD: standard deviation; MCID: minimal clinically important difference; *: from published Literature (Varni et al., 2003); S: small; M: moderate; S-M: small to moderate

Table 2.4: HRQL in relation to neurological outcome: Mean difference in the HRQL domain scores across neurological outcome categories

HRQL Domains	Neurological Outcome Category	Unadjusted scores		Adjusted scores*	
		Mean difference in the HRQL scores (95% CI)	p-value	Mean difference in the HRQL scores (95% CI)	p-value
Total score	Global outcome				
	Normal	Ref	…	Ref	…
	Mild deficit	-2.3 (-13.4 to 8.8)	0.7	-2.9 (-14.1 to 8.5)	0.6
	Moderate deficit	-18.9 (-27.1 to -10.1)	<0.001	-16.9 (-25.9 to -7.8)	<0.001
	Severe deficit	-30.2 (-37.8 to -22.5)	<0.001	-30.1 (-38.2 to -22.1)	<0.001
Physical health	Motor outcome				
	Normal	Ref	…	Ref	…
	Mild deficit	-18.9 (-30.7 to -7.16)	0.002	-22.8 (-34.4 to-11.3)	<0.001
	Moderate deficit	-28.6 (-38.0 to -19.3)	<0.001	-33.9 (-44.0 to -23.7)	<0.001
	Severe deficit	-48.9 (-60.4 to -37.5)	<0.001	-50.1 (-61.6 to -38.6)	<0.001
Psycho-social health	Cognition and behaviour outcome				
	Normal	Ref	…	Ref	…
	Mild deficit	-14.1 (-22.3 to -5.9)	<0.001	-13.4 (-21.7 to -5.1)	0.002
	Moderate deficit	-25.6 (-34.4 to -16.8)	<0.001	-24.3 (-33.2 to -15.3)	<0.001
	Severe deficit	-17.1 (-47.5 to 13.3)	0.3	-15.0 (-45.7 to 15.7)	0.3
Psycho-social health	Language production				
	Normal	Ref	…	Ref	…
	Mild deficit	-16.9 (-25.5 to -8.2)	<0.001	-17.0 (-25.5 to -8.6)	<0.001
	Moderate deficit	-17.7 (-26.4 to -9.0)	<0.001	-18.7 (-27.4 to -10.1)	<0.001
	Severe deficit	-26.7 (-42.8 to -10.5)	0.001	-26.2 (-41.8 to -10.6)	0.001
Psycho-social health	Language compre-hension				
	Normal	Ref	…	Ref	…

	Mild deficit	-20.2 (-29.9 to -11.4)	<0.001	-19.5 (-28.7 to -10.3)	<0.001
	Moderate deficit	-24.5 (-36.7 to -12.4)	<0.001	-22.9 (-35.2 to -10.7)	<0.001
	Severe deficit	-22.1 (-40.1 to -4.1)	0.02	-20.4 (-38.2 to -2.6)	0.03

CI: confidence interval; *: adjusted for age at stroke onset, sex and age at assessment; Ref: reference category

Table 2.5: Predictors of total HRQL score after pediatric ischemic stroke: results of univariate and multivariate linear regression analysis

Variable	**Univariate analysis**		**Multivariate analysis**	
	Mean difference in scores (95% CI)	**p-value**	**Mean difference in scores (95% CI)**	**p-value**
Neurological outcome Good (n=34) Poor (n=56)	 Ref -24.7 (-31.2 to -18.3)	 … <0.0001	 Ref -18.3 (-25.3 to -11.3)	 … <0.0001
Seizures at follow-up No (n=80) Yes (n=10)	 Ref -13.8 (-26.3 to -1.4)	 … 0.03		 NS
Residence Urban (n=45) Rural (n=45)	 Ref -9.5 (-17.3 to -1.7)	 … 0.02		 NS
SES index <42.75 (Median score) ≥42.75	 Ref 13.0 (5.5 to 20.6)	 … 0.001	 Ref 9.1 (2.6 to 15.7)	 … 0.007
Age at stroke onset Neonatal (n=36) Presumed perinatal (n=31) Childhood (n=23)	 Ref -11.2 (-20.1 to -2.3) -13.9 (-23.6 to -4.1)	 … 0.015 0.006		 NS
Size of infarction ≤1/3 of cerebral hemisphere (n=68) >1/3 of cerebral hemisphere (n=22)	 Ref -14.0 (-22.9 to -5.1)	 … 0.002		 NS
Site of stroke BG and PV involved (n=38) No BG and PV involvement (n=52)	 Ref 15.0 (7.5 to 22.5)	 … <0.0001	 Ref 8.2 (1.6 to 14.7)	 … 0.02

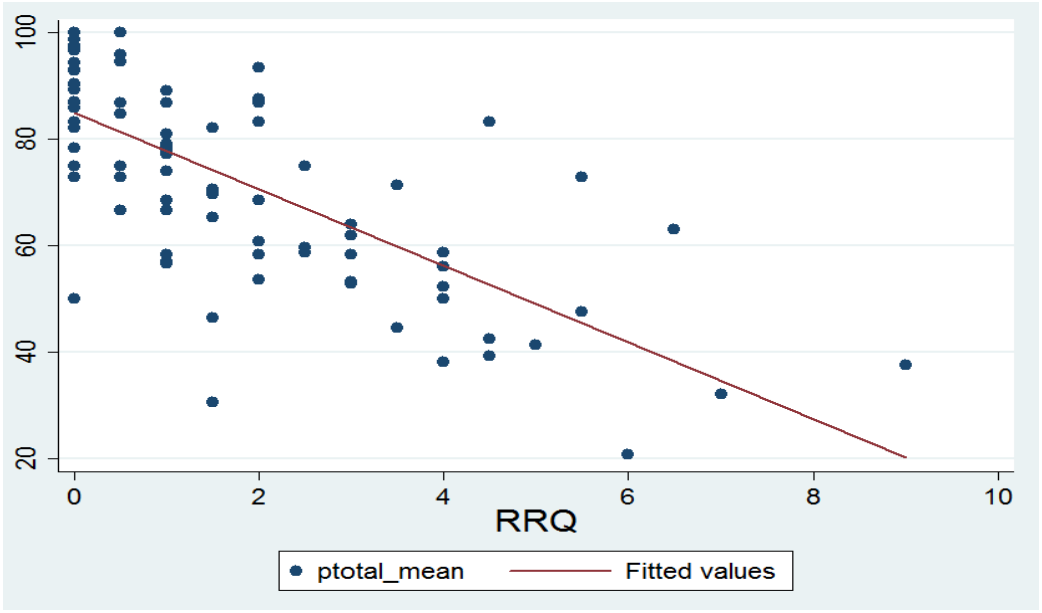
Vascular territory				
PM1 (n=19)	Ref	…		
DM1 (n=7)	21.2 (5.5 to 36.9)	0.009		
AT (n=12)	23.8 (10.7 to 36.9)	0.001		
PT (n=24)	17.6 (6.6 to 28.5)	0.002		
LLS (n=11)	8.4 (-5.1 to 21.8)	0.221		
PVI (n=8)	10.5 (-4.5 to 25.5)	0.17		
Non-cerebral (n=9)	18.4 (4.1 to 32.8)	0.01		

Adjusted R^2= 50%

Sex, age at assessment, time elapsed since stroke, ethnicity, comorbidity, number of children in the family: not significant

CI: confidence interval; Ref: reference category; NS: not significant; SES: socioeconomic status; BG: basal ganglion; PV: periventricular; PM1: proximal middle cerebral artery (MCA); DM1: distal MCA; AT: anterior trunk (superior MCA divison); PT: posterior trunk (inferior MCA divison); LLS: lateral lenticulostriate; PVI: periventricular venous infarction. Vascular territories were defined according to published resources (Kirton etal., 2008)

Figure 2.1: HRQL in relation to neurological outcome



Unadjusted β(HRQL) : -7.2 ($p<0.001$)

Adjusted β(HRQL) : -6.9 ($p<0.001$)

Chapter Three: Age of Stroke Onset Influences the Long Term Clinical Outcome and Health Related Quality of Life in Pediatric Ischemic Stroke Survivors

Pediatric stroke, once considered rare, is increasingly being recognized. The reported frequency of pediatric stroke is greater than 3.0/100,000; an incidence equal to that of childhood cancer (Lynch et al., 2002). Stroke in pediatrics occurs across an age spectrum that includes not only infants, but also the developing brain of the fetus and newborn. In fact, the perinatal period is recognized as one of the most vulnerable times in life to suffer a stroke. With an incidence ranging between 1 in 2300 to 1 in 5000 live births, the ischemic perinatal stroke has been established as the leading known case of cerebral palsy (Raju et al., 2007).

Depending upon the age of onset, pediatric stroke is classified into perinatal and childhood stroke. According to a recent consensus based classification system, perinatal stroke is defined as a vascular event causing focal interruption of blood supply, and occurring between 20 weeks of fetal life through the 28th postnatal day, and confirmed by neuroimaging (Raju et al., 2007; Lynch, 2009). Perinatal stroke is further sub-classified into neonatal and presumed perinatal stroke. Neonatal stroke has its onset from the time of birth to 28 days of age. A diagnosis of presumed perinatal stroke is made when an infant has, what appears to be a normal neonatal course, and usually presents in the first 18 months of life, often showing focal signs of hemiplegia. Post-perinatal neuroimaging reveals chronic changes suggestive of a vascular event involving one of the middle cerebral arteries, or the periventricular region. Given that there had been no historical event suggestive of a stroke during the childs' life, it is presumed to have occurred prior to birth. Childhood stroke is described as occurring between 28 days and 18 years of age (Lynch et al., 2002).

Since stroke in pediatrics occurs during different phases of brain development, age of onset of stroke may affect the mode and extent of brain damage, influencing the clinical outcome and recovery, and therefore the health related quality of life (HRQL) of survivors. There have been conflicting reports on the relationship between age of onset of stroke and clinical outcome. Some authors support the notion of higher vulnerability (i.e. early brain is more sensitive to insult), while others favour the hypothesis of plasticity (i.e. greater chance of recovery after an early injury) (Hebb, 1942; Huttenlocher & Dabholkar, 1997). Literature to date suggests that children with early brain injury (before 1 or 2 years of age) demonstrate poor neurocognitive and motor

outcomes (Anderson et al., 2009; Max et al., 2010; Chapman et al., 2003; Ganesan et al., 2000). In contrast, another study indicated better outcome after neonatal than childhood stroke (deVeber et al., 2000). However, none of these studies have differentiated between acute neonatal and presumed perinatal stroke patients and have also often reported a heterogenous patient population with variable underlying brain pathology.

Currently, there is a paucity of literature on the effect of age of onset of stroke on the long term HRQL of pediatric stroke survivors. HRQL is increasingly acknowledged as an important outcome indicator in chronic diseases, such as stroke. In comparison to the traditional outcome measures on morbidity, HRQL provides a comprehensive assessment of the health status of an individual inclusive of their physical, mental and social well-being, a concept that conforms to the WHO definition of health. Being a patient-reported health status measure, HRQL plays a vital role in the assessment of health care needs of the community and thus, has important implications for health care delivery and resource allocation (Marshall et al., 2006).

We therefore sought to determine the influence of age of onset of pediatric ischemic stroke on neurological outcome, and HRQL using the consensus based defintions for classification of pediatric stroke. This information can identify subgroups with relatively poor perceived health and can provide valuable insight into designing interventions needed to improve their situations and avert more serious consequences.

Methodology

Study population:

A cross sectional study was performed at the Stollery Children's Hospital, Edmonton, Alberta, Canada, a tertiary care pediatric hospital catering to and receiving referrals from a major region in Western Canada (whole of Northern Alberta, parts of Saskatchewan and Manitoba). Children diagnosed with pediatric ischemic stroke between January 2003 and June 2012 were considered for participation if: (1) the child was age 2-18 years at assessment; and (2) at least 1-year follow-up had occurred after childhood stroke. The diagnosis of ischemic stroke was confirmed on MRI or CT scan in all patients. A cut-off age of 2 years was selected as HRQL is difficult to evaluate in very young infants, and there are very few HRQL tools available for infants and small children. A minimum of 1-year of follow-up was decided for childhood stroke

patients to allow the peak period of neurological recovery to occur following the onset of stroke so as to have a fair assessment of the long term outcome and HRQL after pediatric stroke. For this study, children with global brain injury, watershed infarcts, intracranial hemorrhage, cerebral sinovenous thrombosis, transient ischemic attacks, underlying genetic syndromes, or other associated brain pathologies or neurological comorbidity e.g., autism were excluded. The study was approved by the Health Research Ethics Board at the hospital.

Parents of all eligible children were recruited either during routine pediatric stroke clinics or over the telephone. After obtaining an informed consent, all study participants were provided with, or mailed a set of standardized questionnaires. To ensure a uniform assessment and prevent any bias related to the mode of administration, all participants were given a paper copy of the survey, advised to complete it at home and mail it back.

Neurological outcome:

Neurological outcome and need of on-going rehabilitative health care services was assessed at the same time HRQL assessment was performed by using the Pediatric Stroke Recurrence and Recovery Questionnaire (RRQ) completed by the parent (Lo et al., 2012). The RRQ has been adapted from the Pediatric Stroke Outcome Measure (PSOM) to assess the post stroke neurological function and has been validated recently. The RRQ measures the neurological impairment across 5 categories: right sensorimotor, left sensorimotor, cognition/behavior, language production and language comprehension. The neurological deficits in each category are scored as 0 (no neurological deficit with no loss of function), 0.5 (mild deficit, normal function), 1 (moderate deficit with decresed function) or 2 (severe deficit with complete absence of function). A global neurological outcome is also reported as normal (0 score in all 5 categories), mild deficit (0.5 score in only 1 category), moderate deficit (score of 0.5 in 2, 3, or 4 categories; or 1 in 1 category; or 1 in 1 category plus 0.5 in 1 category) or severe deficit (score of 0.5 in all 5 categories; or 1 in 2 categories; or 1 in 1 category plus 0.5 in 2 categories; or 2 in 1 category) (Neuner et al., 2011).

HRQL assessment:

HRQL was evaluated using proxy report versions of the Pediatric Quality of Life Inventory (PedsQL4.0) (Varni et al., 2003). PedsQL is the most widely used generic HRQL measure in children. The instrument contains 23 items encompassing 4 areas: physical, emotional, social and school. Participants respond on a Likert scale from 0-4. Items are reverse scored and linearly transformed to a 0-100 scale with higher converted scores indicating better HRQL. The instrument provides four domain scores, two summary scores (physical and psychosocial functioning) and a total HRQL score. The scale has adequate psychometric properties of reliability and validity (Varni et al., 2003).

Socio-demographic, clinical and radiological data:

Data on the demographic, clinical (age of presentation, side and clinical signs at presentation, underlying risk factors) and neuroimaging features were retrieved from the patient medical records. Neuroimaging, performed as a part of routine clinical procedure on all patients, comprised of sagittal T1-weighted, axial T2-weighted, diffusion weighted and fluid attenuated inversion recovery imaging and were reported by a radiologist and independently reviewed by a pediatric neurologist (JYY). The first MRI obtained after the clinical suspicion of stroke was used to determine the radiological parameters (vascular territory involved, size, site and lateralization of stroke). Vascular territories were defined using the published resources (Kirton et al., 2008). Size was interpreted as an infarct involving less than <1/3, 1/3-2/3 and >2/3 of the ipsilateral cerebral hemisphere. Children were categorized as presumed perinatal, neonatal or childhood stroke, based on historical features and neuroimaging by a pediatric neurologist specialized in stroke. A four factor index of social status was used to determine the socioeconomic status through the information obtained via a parental questionnaire on parents' education, occupation and marital status (Hollingshead, 1975). Information on residence was also obtained through a parental questionnaire.

Statistical Analysis:

Statistical analysis was performed using the STATA version12. Categorical and continuous variables were expressed as proportions and means/medians, respectively. Chi-square/Fisher exact test and linear regression were used to compare the neurological outcome and HRQL data respectively across three groups. HRQL scores were compared with the

published US norms using unpaired student t-test, Z-scores and effect sizes. Effect sizes were interpreted as small (0.20 to 0.49), moderate (0.50 to 0.79) and large (>0.80) based on Cohen's recommendations (Cohen., 1988). A univariate logistic regression analysis was performed for neurological outcome predictors and results were expressed as odds ratio (OR) with 95% confidence intervals (CI). For the purpose of logistic regression, the neurological outcome was dichotomized as good (none or mild impairment) or poor (moderate and severe impairment). A multivariate logistic regression analysis was conducted to identify predictors of the neurological outcome. Variables were selected for a multivariate analysis based on their clinical importance and statistical significance ($p<0.10$). Since age at onset of stroke correlates with clinical signs and risk factors, in a virtually one to one fashion, only age was included in the multivariate model. Vascular territory was not included due to sample size limitations. The prognostic accuracy of the model was estimated using area under the receiver-operating characteristic (ROC) curve. All tests of significance were two-sided and statistical significance was defined as $p<0.05$.

Results

Ninety pediatric ischemic stroke [Presumed perinatal=34% (31), neonatal=40% (36), and childhood=26% (23)] patients were enrolled. The baseline demographic, clinical and radiological parameters of all patients are presented in Table 3.1. Since the exact age of onset of stroke could not be ascertained in the presumed perinatal stroke group of patients, we utilized a time of zero (0) days. Median time elapsed since stroke was comparable in all the three categories. In contrast to a male predominance in neonatal and presumed perinatal stroke patients, a slight female preponderance was identified in the childhood stroke category.

The three groups varied in terms of their clinical presentation, underlying risk factors, size and site of stroke and the vascular territory involved. The mode of clinical presentation was significantly different across the three categories with the majority of neonatal stroke patients (92%) presenting with seizures, whereas those with presumed perinatal stroke having motor deficits (91%) as the chief complaint, consistent with previous reports (Lynch, 2009). Patients with childhood stroke had a variable presentation with motor deficits and seizures in 44% and 22% patients, respectively.

Potential risk factors for stroke were identified in 75% of the neonatal stroke patients and included: labor and delivery complications (n=6), thrombophilia (n=6), congenital heart disease (n=4), meconium aspiration (n=3), birth asphyxia (n=2), twins (n=2), preeclampsia (n=2), maternal smoking (n=1), maternal diabetes (n=1), intrauterine growth retardation (n=1) and infection (n=1). In contrast, no etiology could be documented in over half (52%) of the presumed perinatal stroke patients. In the remaining presumed perinatal strokes, risk factors included antenatal bleeding (n=3), thrombophilia (n=2), twins (n=2) preeclampsia (n=2), maternal diabetes (n=2), smoking (n=1), oligohydraminos (n=1) and antenatal trauma (n=1). About 87% of the childhood stroke patients had an underlying condition or illness contributing to stroke with congenital heart disease reported in up to 44% (n=10) patients. Others had arteriopathy (n=4), infection (n=3), arrhythmia (n=1), and thrombophilia (n=1).

Over 80% of the neonatal and childhood stroke patients were determined to have an infarction involving less than one-third of the cerebral hemisphere, whereas the patients with presumed perinatal stroke had relatively large infarction sizes. The basal ganglia and periventricular involvement was also more evident in presumed perinatal stroke (61%) patients than childhood (44%) and neonatal stroke patients (25%). In terms of vascular involvement, the presumed perinatal stroke group tended to involve more of Proximal M1 of middle cerebral artery and Periventricular regions. In neonatal stroke patients, the most common vascular territory involved was the posterior trunk of the middle cerebral artery (39%). Cortical involvement was comparable in the three groups.

Almost half (47%) of the neonatal stroke and one-third (30%) of the childhood stroke patients had no residual impairments. In contrast, 97% of presumed perinatal stroke patients demonstrated long-term morbidity. Patients with presumed perinatal stroke demonstrated the worst global ($p=0.002$) and sensorimotor outcome ($p=0.001$) and least independence in daily activities ($p=0.001$) compared to the other two groups (Table 3.2). However, the three groups did not differ significantly with respect to cognitive, behavioural and language outcomes. Patients with presumed perinatal stroke also had the maximum need for rehabilitative services at 4 years following the onset of stroke.

Overall HRQL scores were significantly higher in patients with neonatal stroke compared to the other two groups ($p=0.007$) (Table 3.3). Physical ($p=0.001$) and social functioning

(p=0.02) was also found to be better in the neonatal stroke patients, compared to presumed perinatal or childhood stroke groups. Scores in the psychological and school functioning domain were also higher in patients with neonatal stroke, although the results did not reach statistical significance. Emotional functioning was comparable between the 3 groups. Presumed perinatal and childhood stroke patients had comparable scores in all HRQL domains. On comparison to the published norms, neonatal patients achieved comparable scores in all except the emotional functioning domain, where they demonstrated a significantly lower score and a moderate effect size (Table 3.4). Both presumed perinatal and childhood stroke patients had significantly lower scores in all HRQL domains in comparison to the reference population. Parents reported relatively larger deficits after childhood stroke than presumed perinatal stroke indicating more impairment in the HRQL after childhood stroke.

Of the 90 patients, 38% (34) and 62% (56) patients had good and poor neurological outcomes, respectively. The variables associated with poor neurological outcome after pediatric ischemic stroke are listed in table 3.5. In the multivariate analysis, age at stroke onset, location and size of stroke were found to be predictors of neurological outcome in pediatric ischemic stroke survivors. The area under the ROC curve was 0.80, indicating strong predictive ability. (Tape)

Discussion

Since stroke in children may occur at different developmental stages, this study compared the impact of age of onset of stroke on clinical outcome and HRQL of pediatric ischemic stroke survivors using a consensus classification system and validated outcome measures. The study observations clearly indicate that age at stroke onset has serious and direct implications relating to the long-term clinical outcome and HRQL of pediatric ischemic stroke survivors. We demonstrated that presumed perinatal stroke patients have the worst clinical outcome in the long term and neonatal stroke patients exhibit the best long-term HRQL. We also showed that age of onset of stroke is an important prognostic marker of the long-term neurological outcome by multivariate analysis in pediatric ischemic stroke patients.

Importantly, this is the first study to compare parent reports on long-term outcome and HRQL. We demonstrated that the presumed perinatal patients have the worst possible prognosis

in the long-term among three stroke categories. Almost half of the neonatal stroke and one-third of the childhood stroke patients had normal global outcome. In contrast, presumed perinatal stroke patients demonstrated highest morbidity. In addition, they also exhibited the least independence in daily activities and a greater perceived need for rehabilitative health care services in long-term indicating the impact on resource utilization. Further, since these morbidities were assessed at a median follow up of 4.1 years, it is likely that these impairments will last a lifetime and therefore, will amplify the burden on family, society and health care.

HRQL assessment in the current study provided important adjuvant information as it was found to be variably impacted across three age categories. According to the parent proxy reports, neonatal stroke patients demonstrated the highest HRQL in multiple domains among three age groups. Parents of presumed perinatal and childhood stroke patients perceived the HRQL of their children to be quite inferior compared to the neonatal stroke population and reference normal population. Parents also reported a lower HRQL after childhood stroke than presumed perinatal stroke. However, this interpretation is limited by the lack of age-matched controls in the reference population.

Previous literature has described associations between outcome and stroke size and location. Large stroke size, bilateral infarcts and involvement of basal ganglia have been linked with the poor outcome (Mercuri et al., 1999; Boardman et al., 2005). We established a host of predictors of long-term neurological outcome in paediatric ischemic stroke patients by using standardized measures. In the multivariate analysis, we were able to demonstrate that age at stroke remained an important predictor of long-term outcome adjusting for location and size of the lesion.

The study results also indicated a bimodal relationship between the age of onset of stroke and neurological outcome and HRQL of pediatric stroke patients. The clinical outcome and HRQL is inferior after presumed perinatal stroke, improves after neonatal injury and worsens again after an injury to the childhood brain. This bimodal relationship between age of stroke onset and outcome established in the current study is contradictory to the published reports suggesting more damage after an early brain injury and a linear relationship between the age of brain injury and neurocognitive outcome (Anderson et al., 2009; Max et al., 2010; Chapman et al., 2003; Ganesan et al., 2000). However, our study results are more consistent with the

knowledge of brain maturation, which has been described to occur in a step-wise manner, with critical maturation periods, separated by more stable periods (Casey et al., 2000, Gogtay et al., 2004). This phenomenon is also supported by the animal models, which propose a non-linear relationship between the age of brain injury and recovery (Kolb et al., 2004).

Of note, the differential outcome across three age categories was only documented in the global and sensorimotor domains with no differences elicited in cognition, behaviour and language sectors. This may be attributed to the comparable cortical involvement in the three types of stroke. This similar cognitive outcome across different age categories demonstrated here is in contrast to the reports published before suggesting more cognitive impairment after an early brain injury (Anderson et al., 2009). However, a direct comparison across different reports is difficult owing to the heterogenous patient population and different study characteristics. Further, the lack of formal cognitive testing may have underestimated the extent of cognitive and language impairment in the current study.

Further, age at stoke onset was not only found to modulate the clinical recovery but also determine the distribution and severity of brain injury and hence, the clinical presentation. The data suggests that the patients with presumed perinatal stroke tended to have a relatively large size of stroke and had a preference to involve deep grey matter structures and corresponding vascular territories. This kind and extent of brain injury could account for the pronounced motor morbidity documented in these patients. However, the underlying mechanism accounting for differential brain involvement remains to be elucidated. One plausible hypothesis could be the high vulnerability and disruption of the critical neurodevelopmental process responsible for motor development after in-utero stroke. However, the preferential involvement of the deep grey matter structures in presumed perinatal stroke patients prompts a need to recognize the underlying pathophysiological mechanisms in which in-utero animal models of stroke could plausibly provide an important insight.

We also found that the underlying risk factors vary by the age of onset of stroke. A potential risk factor could be identified in 75% of the neonatal and 87% of the childhood stroke patients. In contrast, no underlying etiology could be elicited in more than half of the presumed perinatal stroke patients. A number of risk factors have been linked to presumed perinatal stroke in the literature (Kocaman & Yilmaz, 2012; Golomb et al., 2001). However, their interpretation

is limited by the retrospective nature of study design similar to our study. This suggests a need for prospective and case control studies to explore and provide more conclusive evidence about the etiological factors so that the potential morbidity linked to presumed perinatal stroke could be averted.

The limitations of the study included a modest sample size. This is, however, not unusual in a prospective study of a relatively uncommon population and with a long term follow-up and survey based design. Nevertheless, the data on morbidity, clinical and radiological characteristics is comparable to previously published literature (Ganesan et al., 2000; Golomb et al., 2001; Lee et al., 2005; Wu et al., 2004).

Table 3.1: Sociodemographic, clinical and radiological characteristics of pediatric ischemic stroke patients according to the age at stroke onset

Parameter	**Presumed Perinatal stroke (n=31)**	**Neonatal Stroke (n=36)**	**Childhood stroke (n=23)**	**p-value**
Age at stroke onset (years) Median (IQR) Mean± SD (Range)	ND	0.5 (0-3) days 2.3±4.0 (0-21) days	3.7(0.6-10) 5.2±4.9 (0.2-14)	
Male female ratio	1.8	1.4	0.8	NS
SES score Mean± SD (Range)	44.1±11.6 (15-66)	42.4±13.1 (9-63.5)	38.7±12.9 (13-61)	NS
Time elapsed since stroke (Years) Median (IQR) Mean± SD (Range)	4.1 (2.9-6.2) 5.2±3.4 (2.1-15.2)	4.2 (3.1-7.0) 5.2±3.0 (2.4-15.1)	4.1 (2.0-7.2) 4.6±2.9 (1.0-10.7)	NS
Age at assessment (Years) Median (IQR) Mean± SD (Range)	4.1 (2.9-6.2) 5.2±3.4 (2.1-15.2)	4.2 (3.1-7.0) 5.2±3.0 (2.4-15.1)	10.4(3.3-15.1) 9.8±5.8 (2.2-17.9)	<0.001
Side of clinical presentation Right Left Bilateral Asymptomatic	58.1% (18) 32.3% (10) 6.5% (2) 3.2% (1)	47.2% (17) 25% (9) 19.4% (7) 8.3% (3)	26.1% (6) 47.8% (11) 21.7% (5) 4.4% (1)	NS
Clinical signs at presentation Motor deficit Seizures Other Asymptomatic	90.3% (28) 0 6.5% (2) 3.2% (1)	0 91.7% (33) 5.5% (2) 2.8% (1)	43.5% (10) 21.7% (5) 30.4% (7) 4.4% (1)	<0.001
Risk factors Maternal Child None Congenital heart disease	35.5% (11) 12.9% (4) 51.6% (16) 6.5% (2)	22.2% (8) 52.8% (19) 25.0% (9) 11.1% (4)	0 87.0% (20) 13.0% (3) 43.5% (10)	<0.001 0.002
Lateralization of stroke Right Left Bilateral	35.5% (11) 61.3% (19) 3.2% (1)	36.1% (13) 47.2% (17) 16.7% (6)	56.5% (13) 26.1% (6) 17.4% (4)	NS
Size of infarction				

<1/3 of cerebral hemisphere	64.5% (20)	80.6% (29)	82.6% (19)	0.04
1/3-2/3	32.3% (10)	16.7% (6)	4.4% (1)	
>2/3	3.2% (1)	2.8% (1)	13% (3)	
Site of infarction				
BG and PV involvement	61.3% (19)	25% (9)	43.5% (10)	
Cerebral with no BG and PV involvement	38.7% (12)	63.9% (23)	34.8% (8)	0.003
Non-cerebral	0	11.1% (4)	21.7% (5)	
Cortical	64.5% (20)	80.6% (29)	56.5% (13)	NS
Non-cortical	35.5% (11)	19.4% (7)	43.5% (10)	
Vascular territory Involved				
PM1	25.8% (8)	16.7% (6)	21.7% (5)	
DM1	9.7% (3)	8.3% (3)	4.4% (1)	
AT	3.2% (1)	16.7% (6)	21.7% (5)	0.002
PT	25.8% (8)	38.9% (14)	8.7% (2)	
LLS	12.9% (4)	5.6% (2)	21.7% (5)	
PVI	22.6% (7)	2.8% (1)	0	
Non-cerebral	0	11.1% (4)	21.7% (5)	

ND: can not be determined; SD: standard deviation; IQR: interquartile range; SES: socioeconomic status; BG: basal ganglion; PV: periventricular; NS: Not significant; PM1: proximal middle cerebral artery (MCA); DM1: distal MCA; AT: anterior trunk (superior MCA divison); PT: posterior trunk (inferior MCA divison); LLS: lateral lenticulostriate; PVI: periventricular venous infarction. Vascular territories were defined according to published resources (Kirton etal., 2008)

Table 3.2: Parent perception of the long-term clinical outcome and need of rehabilitative health care services according to the age of stroke onset

Parameter	**Presumed Perinatal stroke (n=31)**	**Neonatal Stroke (n=36)**	**Childhood stroke (n=23)**	**p-value**
Global outcome • Normal • Mild deficit • Moderate deficit • Severe deficit	 3.2% (1) 12.9% (4) 41.9% (13) 41.9% (13)	 47.2% (17) 11.1% (4) 8.3% (3) 33.3% (12)	 30.4% (7) 4.4% (1) 34.8% (8) 30.4% (7)	 <0.001
Sensorimotor outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 3.2% (1) 19.4% (6) 54.8% (17) 22.6% (7)	 55.6% (20) 13.9% (5) 22.2% (8) 8.3% (3)	 43.5% (10) 13% (3) 21.7% (5) 21.7% (5)	 <0.001
Cognition and Behaviour outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 58.1% (18) 22.6% (7) 16.1% (5) 3.2% (1)	 66.7% (24) 19.4% (7) 13.9% (5) 0	 60.9% (14) 17.4% (4) 21.7% (5) 0	 NS
Language production outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 54.8% (17) 19.4% (6) 22.6% (7) 3.2% (1)	 63.9% (23) 19.4% (7) 13.9% (5) 2.8% (1)	 52.2% (12) 17.4% (4) 21.7% (5) 8.7% (2)	 NS
Language comprehension outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 74.2% (23) 12.9% (4) 9.7% (3) 3.2% (1)	 80.6% (29) 13.9% (5) 2.8% (1) 2.8% (1)	 65.2% (15) 17.4% (4) 13% (3) 4.4% (1)	 NS
Bilateral sensorimotor impairment	2.4% (2)	2.8% (3)	1.8% (2)	NS
Independence	29% (9)	75% (27)	61% (14)	0.001
On-going need of AEDs	12.9% (4)	11.1% (4)	8.7% (2)	NS
On-going Rehabilitation • Physical therapy • Occupational therapy • Speech therapy • Special education services	 77.4% (24) 67.7% (21) 38.7% (12) 29% (9)	 19.4% (7) 27.8% (10) 13.9% (5) 13.9% (5)	 26.1% (6) 26.1% (6) 17.4% (4) 8.7% (2)	 <0.001 0.001 0.05 NS

AEDs: antiepileptic drugs; NS: not significant

Table 3.3: Parent perception of the long term HRQL according to the age of stroke onset

HRQL Parameters	Presumed Perinatal stroke (n=31)	Neonatal Stroke (n=36)	Childhood stroke (n=23)	p-value
Total HRQL score	68.8±15.4	80.0±17.8	66.1±22.3	0.007
Physical functioning score	67.1±20.3	85.1±21.5	64.8±34.0	0.001
Psychological functioning score	70.3±14.6	77.3±18.5	67.3±19.8	0.07
Emotional functioning score	71.1±20.3	71.5±22.5	65.4±20.7	NS
Social functioning score	70.2±16.2	81.0±19.7	68.3±22.0	0.02
School functioning score	68.1±16.9	79.3±20.7	67.8±25.6	0.08

Results are expressed as Mean±SD

Table 3.4: HRQL of pediatric ischemic stroke survivors compared to reference population

HRQL domains	Ref scores (Mean ± SD)	Neonatal stroke vs Ref			Presumed perinatal stroke vs Ref			Childhood stroke vs Ref		
		p-value	Z-score	ES	p-value	Z-score	ES	p-value	Z-score	ES
Total HRQL score	81.34 ± 15.92	NS	-0.08		<0.0001	-0.79	L	0.003	-0.96	L
Physical F	83.26 ± 19.98	NS	0.09		<0.0001	-0.81	L	0.01	-0.92	L
Psycho-logical F	80.22 ± 15.84	NS	-0.18		0.0005	-0.63	M	0.0001	-0.82	L
Emotional F	80.28 ± 16.99	0.03	-0.52	M	0.003	-0.54	M	<0.0001	-0.88	L
Social F	82.15 ± 20.08	NS	-0.06		0.0009	-0.60	M	0.001	-0.69	M-L
School F	76.91 ± 20.16	NS	0.12		0.02	-0.44	S-M	0.03	-0.45	S-M

Ref: reference population; ES: effect size; F: functioning; NS: not significant; S: small; M: moderate; L: large; S-M: small to moderate; M-L: moderate to large

Table 3.5: Predictors of poor neurological outcome after pediatric ischemic stroke

Variable	**Univariate analysis**		**Variables selected for multivariate analysis**	**Multivariate analysis**	
	Odds Ratio (95% CI)	**p-value**		**Odds Ratio (95% CI)**	**p-value**
Age at stroke onset			In		
Neonatal (n=36)	Ref	…		…	…
Presumed perinatal (n=31)	7.28 (2.3-23.3)	0.001		5.1 (1.4-19.0)	0.02
Childhood (n=23)	2.63 (0.9-7.8)	0.08		1.9 (0.6-6.5)	0.3
Sex			Out		
Male (n=51)	Ref	…			
Female (m-39)	0.53 (0.2-1.3)	0.15			
SES score			In		
<42.75 (Median score)	Ref	…			NS
≥42.75	0.46 (0.2-1.1)	0.08			
Residence			In		
Urban (n=45)	Ref	…			NS
Rural (n=45)	2.6 (1.1-6.4)	0.03			
Clinical signs			Out		
Motor deficit(n=38)	Ref	…			
Seizures (n=38)	0.06 (0.02-0.2)	0.000			
Other + asymptomatic (n=14)	0.05 (0.01-0.2)	0.000			
Side of clinical presentation			Out		
Right (n=41)	Ref	…			
Left (n=30)	1.08 (0.4-3.0)	0.9			
Bilateral (n=14)	0.27 (0.09-0.9)	0.03			
Risk factors			Out		
Maternal (n=19)	Ref	…			
Child (n=43)	0.25 (0.06-0.9)	0.05			
None (n=28)	0.23 (0.06-0.9)	0.05			
Size of infarction			In		

≤1/3 of cerebral hemisphere (n=68) >1/3 of cerebral hemisphere (n=22)	Ref 5.3 (1.4-19.6)	… 0.01		… 4.8 (1.1-21.2)	… 0.04
Site BG and PV involved (n=38) No BG and PV involvement (n=52)	 Ref 0.27 (0.1-0.7)	 … 0.006	In	 … 0.49 (0.2-1.5)	 NS
Vascular territory PM1(n=19) DM1 (n=7) AT (n=12) PT (n=24) LLS (n=11) PVI (n=8) Non-cerebral (n=9)	 Ref 0.04 (0-0.5) 0.01 (0-0.1) 0.09 (0.01-0.8) 0.07 (0.01-0.7) 0.17 (0.01-2.2) 0.11 (0.01-1.3)	 … 0.01 0.00 0.03 0.02 0.17 0.08	Out		

Area under the ROC curve = 0.80

Lateralization, age at assessment, time elapsed since stroke were not found to be significant on univariate analysis.

CI: confidence interval; Ref: reference category; NS: not significant; SES: socioeconomic status; BG: basal ganglion; PV: periventricular; PM1: proximal middle cerebral artery (MCA); DM1: distal MCA; AT: anterior trunk (superior MCA divison); PT: posterior trunk (inferior MCA divison); LLS: lateral lenticulostriate; PVI: periventricular venous infarction. Vascular territories were defined according to published resources (Kirton etal., 2008)

Chapter Four: Comparison of Self and Proxy Reports on Health Related Quality of Life of Pediatric Ischemic Stroke Population

HRQL is being increasingly accepted as an important outcome measure in health care and delivery. Being a patient based subjective measure, the concept of HRQL has gained increased popularity over the last few decades. These patient-reported outcome measures are acknowledged as vital instruments for evaluation of health care needs of a community, resource allocation, planning and health policy making, and prioritization of health care and social support services (Marshall et al., 2006). Further, these tools have an indispensible role to play in the evaluation of health care services, measurement of intervention outcomes and comparison of treatment costs and benefits.

HRQL is also increasingly acknowledged as an important outcome indicator in children (Morris et al., 2009; Ingerski et al., 2010). However, HRQL assessment in children differs from adults in some aspects. In children, the concept of HRQL further expands to involve family, friends, school and environment in addition to physical, social and emotional domains of health. Thus, HRQL in children arises from a dynamic relationship among all elements. There are developmental considerations as well as the concept of HRQL changes over time. This makes assessment of the HRQL much more difficult in pediatric population than adults.

Further, unlike the majority of adults, where self-report is the standard method for assessment of HRQL, parent proxy assessment of HRQL is much more commonly employed in children because of young age and cognitive immaturity. However, parents may perceive the HRQL of their children quite differently from what is perceived by children themselves. This may result in a lack of concordance between two (Varni et al., 1999). However, it is vital to have both self and proxy assessment as it is important to understand both perspectives. These may provide complementary information that can influence care.

Proxy evaluation of HRQL is of paramount importance in pediatric stroke patients with cogntitve disabilities and younger age at the onset of stroke. To date, both self and proxy assessment of the HRQL of pediatric stroke survivors is reported in some studies. ((O'Keeffe et al., 2012; Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg 2010; Everts et al., 2008; Friefeld et al., 2004). Limited data are available on the correlation of both reports (O'Keeffe et al., 2012; Neuner et al., 2011; Christerson & Stromberg 2010; Friefeld et al., 2004).

Further, present studies are limited in their methodology and interpretation of the HRQL data, which should be assessed for both statistical significance and clinical importance to appropriately guide the health improving interventions (O'Keeffe et al., 2012; Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg 2010; Everts et al., 2008; Simma et al., 2007; Friefeld et al., 2004; Han et al., 2004; Gordon et al., 2002). Clear and detailed reporting of such data is also vital since this is only way to understand patient perspective. Hence, in this study, we evaluated the HRQL of pediatric ischemic stroke patients using both self and proxy report forms. In addition, HRQL data were analysed using measures recommended for interpretation and reporting of patient reported outcome (PRO) data (Revicki et al., 2007).

Methodology

Study population:

A cross sectional study was conducted at the Stollery Children's Hospital, Edmonton, Alberta, Canada. Children diagnosed with ischemic stroke between January 2003 and June 2012 were included in the study if: (1) aged 5-18 years at assessment; and (2) at least 1-year had occurred after childhood stroke to allow the peak period of neurological recovery and thus, to have a fair assessment of the long-term HRQL after pediatric stroke.. The diagnosis of ischemic stroke was made on MRI or CT scan in all patients. A cut-off age of 5 years was selected as children over 5 can reliably report their own HRQL (Varni et al., 2007). Children with global brain injury, watershed infarcts, intracranial hemorrhage, cerebral sinovenous thrombosis, transient ischemic attacks, underlying genetic syndromes, or other associated brain pathologies or neurological comorbidity e.g., autism were excluded from the study. The study was approved by the Health Research Ethics Board at the hospital.

All eligible children and their caregivers were recruited either during routine pediatric stroke clinics or over the telephone. After obtaining an informed consent from parents and assent from children, all study participants were provided with, or mailed a set of standardized questionnaires. All participants were given a paper copy of the survey, advised to complete it at home and mail it back.

Neurological outcome assessment:

Neurological outcome was assessed using the Pediatric Stroke Recurrence and Recovery Questionnaire (RRQ), a tool developed from the Pediatric Stroke Outcome Measure (PSOM) to assess the post stroke neurological function and recovery (Lo et al., 2012). The RRQ was completed by the parents. The instrument assesses the type and degree of neurological impairment across 5 categories: right sensorimotor, left sensorimotor, cognition/behavior, language production and language comprehension. The neurological deficits in each category are scored as 0 (no neurological deficit with no loss of function), 0.5 (mild deficit, normal function), 1 (moderate deficit with decreased function) or 2 (severe deficit with complete absence of function). In addition, global neurological outcome is also reported as normal (0 score in all 5 categories), mild deficit (0.5 score in only 1 category), moderate deficit (score of 0.5 in 2, 3, or 4 categories; or 1 in 1 category; or 1 in 1 category plus 0.5 in 1 category) or severe deficit (score of 0.5 in all 5 categories; or 1 in 2 categories; or 1 in 1 category plus 0.5 in 2 categories; or 2 in 1 category) (Neuner et al., 2011).

HRQL assessment:

HRQL was evaluated using self and proxy report versions of the Pediatric Quality of Life Inventory (PedsQL4.0) and compared to the US population norms (Varni et al., 2003). PedsQL has adequate psychometric properties of reliability and validity. The instrument has both self and proxy report versions. There are four surveys for different age categories: Toddler (ages 2-4), Young Child (ages 5-7), Child (ages 8-12), and Teen (ages 13-18). Only proxy report is available for the toddler age group. Both self and proxy report versions are available for the other age groups. The instrument has 23 items and a recall period of 1 week. Participants respond on a Likert scale from 0-4. Items are reverse scored and linearly transformed to a 0-100 scale with higher converted scores indicating better HRQL. Four domain scores (physical, emotional, social and school), two summary scores (physical and psychosocial functioning) and a total HRQL score are obtained.

Statistical analysis:

Statistical analysis was performed using the STATA version12. Categorical and continuous variables were expressed as proportions and means/medians, respectively. HRQL data was analysed for statistical significance by comparing the HRQL scores with the published

US norms using unpaired student t-test. Child and proxy reports were compared to child and proxy norms, respectively. In addition, a direct comparison of the self and proxy reports was also performed. Clinical importance was assessed using the norm based approach (Revicki et al., 2007). Norm based strategies involve comparing the data to a normal distribution, which is characterized by a standardized score such as Z-score. Z scores were computed as the difference between the patient sample mean and reference mean, divided by the standard deviation of the reference population. Child and proxy norms from US were used as the reference population (Varni et al., 2003). Effect sizes to assess the magnitude of difference in HRQL scores were also computed using the same formula as Z-score. These were interpreted as small (0.20 to 0.49), moderate (0.50-0.79) and large (>0.80) based on Cohen's recommendations (Cohen., 1988). In literature on HRQL, a difference of one half a standard deviation (0.5 SD) or moderate effect size has been suggested as a minimally important difference (Norman et al., 2003). Thus, a Z-score of 0.5 or moderate effect size would have indicated a clinically important difference in our patient population. The absolute difference in HRQL scores was also compared with the minimal clinically important difference (MCID) published in the literature (Varni et al., 2003). MCID is defined as the smallest difference in the HRQL measure that is perceived to be clinically important in that population.

The correlation between self and proxy reports was assessed using the Pearson and intra class correlation coefficient (ICC). Pearson coefficient is a measure of association between two reports, whereas, ICC measures the agreement between two reports. Agreement is reported as poor for ICC values less than .40, fair for values between .40 and .59, good for values between .60 and .74, and excellent for values between .75 and 1.0 (Cicchetti., 1994).

Results

Thirty two pediatric ischemic stroke patients were enrolled. Baseline demographic information is presented in Table 4.1. The mean age at diagnosis of stroke was 41.6 months (range: neonate to 168.5 months), with male to female ratio of 1.5 (19 males, 13 females). There were 10 (31%) neonatal, 9 (28%) presumed perinatal and 13 (41%) childhood stroke patients, respectively. The mean age at assessment was 10.9 years(range: 5.2-17.9). Average follow-up duration was 7.8 years (range 1-15.2 years). A quarter of the patients had a normal global outcome, whereas 75% had varying degree of neurological deficits (Table 4.2). Motor outcome

was normal in less than one-third of the patients (28%), with moderate to severe impairment in 53% patients.

Table 4.3 presents the self and proxy reported HRQL scores of all 32 patients. Both self and proxy reports revealed lower total HRQL scores in the study population compared to normative data suggesting a lower overall HRQL in pediatric ischemic stroke survivors. Parents demonstrated a statistically significant difference in all domains of PedsQL inclusive of physical and psychosocial domains as well as the emotional, social and school domains of the psychosocial dimension. In contrast, children did not indicate a statistically significant difference in the social functioning domain. Z scores were negative in all domains in both self and proxy reports suggesting a lower HRQL in the patient population compared to published norms. These were in the clinically important range for all domains as indicated in both proxy and self reports. Effect sizes as expressed by parents and children were also significant for all domains. The absolute difference in the HRQL scores of patient and reference population also exceeded the MCID published in the literature in both self and proxy reports. Thus, a clinical important difference was demonstrated in all domains of HRQL in the study population.

Z scores and effect sizes computed from proxy reports were larger than that evident from self-reports in all except the physical and school functioning domain. These results suggest that parents perceived more impairment in the total domain as well as the emotional and social functioning domain of the psychosocial dimension, whereas, children perceived more problems in the physical and school functioning domain. Parents indicated largest effect sizes and maximum impairment in the emotional functioning domain, whereas physical functioning domain was rated to be the most poor by children.

A direct comparison of the proxy and self reports revealed lower mean HRQL scores reported by parents than children in all domains of PedsQL (Table 4.4). This also suggests that parents reported more impairment in the HRQL of their children compared to what was reported by children themselves. This difference between self and proxy report scores were not statistically significant and effect sizes were small. However, the difference in HRQL scores of two reports exceeded the MCID published in the literature in total and psychosocial domains.

When assessed in relation to neurological outcome as measured by the RRQ, parents and children reported different findings (Table 4.5). A significantly lower total HRQL was observed in children with only severe global deficits according to self reports. Children with mild or moderate deficits did not report lower total HRQL. However, in proxy reports, parents reported a significantly lower total HRQL in children with both moderate and severe deficits.

Pearson and Intra class correlation coefficient were found to be the strongest in the physical functioning domain suggesting an excellent degree of agreement in this domain between self and proxy reports (Table 4.6). Agreement was noted to be the least in emotional functioning domain, where the degree of agreement was fair.

Discussion

Since both self and proxy assessment of HRQL is essential in children to better understand their health, the current study focused on a dual assessment of the HRQL of pediatric ischemic stroke population. In addition, we used guidelines recommended for methodological reporting of the patient reported outcome data. Our assessment included detailed reporting of the study population with a clear inclusion and exclusion criteria. HRQL data was analyzed and presented utilizing techniques recommended for the interpretation and reporting of the patient reported outcome data. Results were interpreted for both, the statistical significance and clinical importance of study observations.

In this study, parents reported both a statistically significant and clinically important difference in all domains of HRQL compared to normative data. Children also indicated a clinically important difference in all domains of HRQL. However, they did not report a statistical significant difference in the social functioning domain.

In our study, both self and parent proxy reports demonstrated a lower overall HRQL in pediatric ischemic stroke survivors compared to the reference population, which is consistent with some of the previous reports (Friefeld et al., 2004; Neuner et al., 2011). In contrast, Evert et al. (2008) did not observe a significant difference in the overall HRQL of children with stroke in both children and parent ratings. However, a direct comparison of studies addressing HRQL in survivors of pediatric stroke is difficult because of the clinical heterogeneity of the patient population involved and the variety of measures being used for assessment. Friefeld et al. (2004)

evaluated HRQL in a mixed population of 84 arterial ischemic stroke and 16 cerebral sinus venous thrombosis children using the PedsQL and reported lower total HRQL. Other studies have used different measures such as KINDL-R, KIDSCREEN and CHQ for assessment of HRQL.

Studies on HRQL of pediatric stroke survivors have reported variable findings with respect to the domains affected in parent and child ratings. In some studies, parents and children have reported problems in only selective domains such as emotions, self-esteem, friend related well-being etc. (Neuner et al., 2011; Cnossen et al., 2010; Christerson & Stromberg 2010; Everts et al., 2008). In contrast, our study identified an inferior HRQL in all domains of HRQL including physical, emotional, social and school. The heterogeneity in the patient population, differences in parent perception and cultural differences may have yielded different study findings. This might also be attributed to the fact that none of the existing studies have interpreted the HRQL data for clinically important findings.

We reported that parents perceived more impairment in the HRQL of their children compared to what was perceived by children themselves. We also identified the differences between two reports with respect to the most impaired domain. In another Canadian study, both parents and children reported school functioning domain to be the most impaired (Friefeld et al., 2004). Previous studies have reported physical domain to be the most problematic according to parent proxy reports (Han et al., 2004; Gordon et al., 2002). In our study population, parents rated the emotional domain to be the most affected, whereas children perceived maximum problems in the physical functioning domain. Thus, parents overestimated the degree of emotional disturbance and underestimated the extent of physical impairment relative to their children's self assessment of HRQL. These findings underscore the importance of taking both parent and child perspectives into account in the evaluation of HRQL of pediatric stroke patients.

Our data on correlation coefficients suggest good to excellent agreement between parent and child reports in all except the emotional functioning domain. However, it is still important to consider both viewpoints to better judge the HRQL of these children. The lowest agreement in the emotional functioning domain in our study is consistent with the findings of a systematic review published before (Osier & Morse, 2001).

The study has its own limitations. The study has a small sample size. The study data were compared with the US norms as local pediatric control data were not available. We used a generic questionnaire for assessment of HRQL, as no stroke specific scale is available yet in the pediatric population.

Table 4.1: Demographic parameters of participants (N=32)

Parameter	**Mean±SD (Range)**	**Median (IQR)**
Age at onset of stroke (months)	41.6±58.1 (0-168.5)	0.05 (0-103.4)
Age at assessment (years)	10.9 ±3.9 (5.2-17.9)	10.4 (8.2-14.6)
Time elapsed since stroke (years)	7.8±3.5 (1.0-15.2)	7.7 (5.2-10.2)

SD: standard deviation; IQR: interquartile range

Table 4.2: Neurological outcome of pediatric ischemic stroke survivors

Clinical Outcome	**Pediatric Stroke (n=32)**
Global outcome • Normal • Mild deficit • Moderate deficit • Severe deficit	 25 % (8) 9.4% (3) 31.2% (10) 34.4% (11)
Motor outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 28.2% (9) 18.8% (6) 40.6% (13) 12.5% (4)
Cognition and Behaviour outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 53.1% (17) 25% (8) 21.9% (7) 0
Language outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 62.5% (20) 25% (8) 9.4% (3) 3.1% (1)
Comprehension outcome • No impairment • Mild impairment • Moderate impairment • Severe impairment	 71.9% (23) 18.8% (6) 9.4% (3) 0

Table 4.3: Self and proxy assessment of HRQL of pediatric ischemic stroke survivors

HRQL domains	Mean score	SD	p value	Z-score	Effect size	Absolute Difference	MCID*
Child self-report							
Total score	74.66	19.36	0.02	-0.62	M	8.21	4.36
Physical health	77.54	23.43	0.03	-0.67	M-L	9.32	6.66
Psychosocial health	73.13	19.08	0.03	-0.52	M	7.6	5.30
Emotional functioning	71.25	21.44	0.04	-0.37	S-M	6.96	8.94
Social functioning	76.72	24.35	NS	-0.42	S-M	7.32	8.36
School functioning	71.41	20.37	0.005	-0.50	M	8.51	9.12
Parent proxy-report							
Total score	69.67	20.23	0.003	-0.73	M-L	11.67	4.50
Physical health	73.44	24.95	0.006	-0.49	S-M	9.82	6.92
Psychosocial health	67.66	20.11	0.001	-0.79	M-L	12.56	5.49
Emotional functioning	63.91	24.42	0.0007	-0.96	L	16.37	7.79
Social functioning	71.56	21.61	0.003	-0.53	M	10.59	8.98
School functioning	67.5	21.52	0.008	-0.47	S-M	9.41	9.67

SD: standard deviation; MCID: minimal clinical important difference; *: from published literature; S: small; M: moderate; L: large; S-M: small to moderate; M-L: moderate to large

Table 4.4: Direct Comparison of self and proxy reports

HRQL domains	Self report	Proxy report	P value	Z-score	Effect size	Absolute Difference	MCID*
Total score	74.66	69.67	NS	0.26	S	4.99	4.36
Physical health	77.54	73.44	NS	0.17	S	4.1	6.66
Psychosocial health	73.13	67.66	NS	0.29	S	5.47	5.30
Emotional functioning	71.25	63.91	NS	0.34	S	7.34	8.94
Social functioning	76.72	71.56	NS	0.21	S	5.16	8.36
School functioning	71.41	67.5	NS	0.19	S	3.91	9.12

MCID: minimal clinical important difference; *: from published literature; S: small

Table 4.5: Total HRQL in relation to global neurological outcome: Mean difference in the HRQL domain scores across global outcome categories

HRQL Domains	Neurological Outcome Category	Self reports		Proxy reports	
		Mean difference in the HRQL scores across outcome categories (95% CI)	p-value	Mean difference in the HRQL scores across outcome categories (95% CI)	p-value
Total score	Global outcome				
	Normal	Ref	…	Ref	…
	Mild deficit	1.9 (-23 to 26.8)	NS	-4.4 (-25.9 to 17.1)	NS
	Moderate deficit	-4.6 (-22.1 to 12.9)	NS	-21.8 (-36.9 to -6.8)	0.006
	Severe deficit	-20.2 (-37.4 to -3.1)	0.02	-33.6 (-48.4 to -18.8)	<0.001

CI: confidence interval; Ref: reference category; NS: not significant

Table 4.6: Pearson and Intra class correlation coefficient scores reflecting the correlation between child and parent proxy reports

HRQL Domain	**Pearson correlation coefficient**	**Intra class correlation coefficient**
Total score	0.78	0.76 (0.55-0.88)
Physical health	0.83	0.83 (0.67-0.91)
Psychosocial health	0.71	0.69 (0.44-0.83)
Emotional functioning	0.55	0.53 (0.24-0.74)
Social functioning	0.67	0.66 (0.41-0.82)
School functioning	0.76	0.75 (0.55-0.87)

Chapter Five: Conclusions

The objective of my Masters's thesis project was to systematically evaluate the HRQL and its determinants in survivors of pediatric ischemic stroke. Existing literature on the HRQL of pediatric stroke patients reports a heterogenous patient population encompassing different kinds of stroke including arterial ischemic, sinus venous thrombosis and hemorrhagic stroke. Further, studies are limited in the interpretation and reporting of HRQL data and the measures used for assessment of HRQL vary among different studies.. Clear and thorough reporting of HRQL data is necessary since patient-reported outcome is the only measure of assessing patient's perspective. Interpretation of the HRQL data for clinically significant findings is also imperative to appropriately guide the health improving interventions. In this study, we did a methodological assessment of the HRQL of pediatric ischemic stroke population. Our assessment included detailed reporting of the study population with a clear inclusion and exclusion criteria. We also included clinical outcome as an external anchor and provided detailed information on data collection procedures, methods of analysis and methods of interpretation. Further, HRQL data were analysed using different approaches recommended for the interpretation and reporting of the patient reported outcome data. Results were assessed for both statistically significant and clinically important findings.

In our study, both parents and children reported lower overall HRQL in children with stroke compared to normative data. Results were in the statistically significant and clinically important range for all domains. Further, parents perceived the maximum impairment and lowest HRQL in the emotional functioning domain for their children. Thus, emotional functioning was rated to be the most affected domain by parents. This is contrary to what is perceived by physicians, who report the maximum deficits in sensorimotor domain of pediatric stroke patients. These results have direct implications for providing health care services to pediatric stroke patients as our findings emphasize the importance of having a comprehensive and QOL assessment of these patients. Health care providers need to understand not only the physical, but also the emotional and social aspects of having pediatric stroke. These findings also necessitate the need to develop psychosocial interventions aimed at improving emotional and social functioning of pediatric stroke patients.

Our study demonstrated an inverse linear relationship between HRQL and degree of neurological impairment. We also found that children with low socioeconomic status had worse HRQL. Further, age of onset of stroke seemed to influence neurological outcome and HRQL of pediatric ischemic stroke patients with neonatal stroke patients demonstrating the best HRQL and presumed perinatal stroke patients demonstrating the maximum long-term morbidity. These findings have significant implications for developing health improving interventions and improving the HRQL of pediatric ischemic stroke patients.

Our study also has significant implications with respect to future research as it describes the importance to assess and report HRQL data for clinically important findings. The use of Z scores and effect sizes in future studies would also enable better comparison among different studies and could establish HRQL results from a large homogenous cohort of pediatric stroke.

One of the strengths of our study is a median follow-up of > 4years. Thus, our observations provide a fair assessment of the long-term outcome and HRQL after pediatric ischemic stroke. In addition, proxy measures are being increasingly recognized as important instruments in HRQL and health outcomes research and for designing health care plans and models, as these tools provide parents' perspective about their children health status. In this study, we were successful in achieving a parent perspective, which included both objective and subjective assessments of their children's health status and HRQL.

We acknowledge the limitations of the study. The study has a modest sample size, which is, however, not unusual in a prospective study of a relatively uncommon population and with a long-term follow-up and survey based design. Another limitation was the lack of Canadian pediatric control data. Our study data were compared with the population-based US controls. A third limitation was the utilization a generic HRQL scale in the study as there is no stroke specific HRQL scale available in pediatric age group.

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