Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: March 31, 2023

Citation: Mailo J, Srivastava R, Rajapakse T, Yager JY, 2023. Perinatal Stroke: Clinical Pearls and Future Directions, Medical Research Archives, [online] 11(3). https://doi.org/10.18103/mra.v11i3.3259

DOI: https://doi.org/10.18103/mra.v11i3.3259

ISSN: 2375-1924

REVIEW ARTICLE

Perinatal Stroke: Clinical Pearls and Future Directions

Janette Mailo*, Ratika Srivastava, Thilinie Rajapakse, Jerome Y Yager

Faculty of Medicine & Dentistry - Pediatrics Department, University of Alberta, Edmonton, Canada

*jmailo@ualberta.ca

Abstract

Perinatal strokes are disorders of cerebral vasculature occurring in the developing brain between 20 weeks of gestation and 28 days postnatally[1]. This review describes specific types of perinatal strokes and includes up-to-date risk factors, clinical presentations, outcomes, and management including expert consensus and controversies. We will conclude with a discussion of new research focused on optimizing the quality of life for children with stroke and their families.

Perinatal stroke can present acutely and should be considered for a newborn with unexplained encephalopathy or seizures, particularly those that are focal in nature. Presumed perinatal stroke syndromes present later in infancy with motor and sensory asymmetry. In either case, neuroimaging helps identify a specific perinatal stroke syndrome. Most perinatal stroke survivors experience long-term morbidity, inclusive of cerebral palsy (CP), epilepsy, cognitive and behavioural disabilities, and visual deficits.

Significant progress has been made in understanding cerebrovascular injuries of the developing brain and the role of early rehabilitation in recovery. With limited preventative and acute treatment options available, long-term neurorehabilitation continues to be the focus of treatment. Important too is the need to recognize the significant psychosocial impact of perinatal stroke on the entire family. Online resources and support systems are increasingly available through national and international pediatric stroke organizations.

CLASSIFICATION OF PERINATAL STROKE

Acute symptomatic perinatal strokes are identified in newborns presenting within the first days after a term or near-term birth. These are the most commonly described types of perinatal strokes; therefore, most of the risk factors, diagnostic criteria, and management pathways are based on these. Acute perinatal stroke subtypes include neonatal arterial ischemic stroke (NAIS), neonatal hemorrhagic stroke (NHS), and neonatal cerebral sinovenous thrombosis (CSVT). The remaining perinatal stroke syndromes present in a delayed manner, typically between 4-12 months of age, with early hand preference, other motor asymmetries, or seizures. Subsequent neuroimaging confirms a chronic, remote infarct. These are termed presumed perinatal strokes[2]. Presumed perinatal stroke diseases include arterial presumed perinatal ischemic stroke (APPIS) and periventricular venous infarction (PVI)[3].

NEONATAL ARTERIAL ISCHEMIC STROKE

Neonatal arterial ischemic stroke (NAIS) refers to arterial ischemic strokes that present in term (>37 weeks gestation) neonates within the first 28 days of life. They typically present with mild neonatal encephalopathy (poor feeding, lethargy) and/or focal seizures within the first 48 hours of life. NAIS is the most common type of perinatal stroke[4,5] with an estimated incidence as high as one in 1600 to 3000 live births[6]. This exceeds the incidence of childhood stroke by approximately 10-fold, second only to the incidence of ischemic stroke in the adult population[7,8].

PATHOPHYSIOLOGY AND RISK FACTORS

Pathophysiological mechanisms of perinatal arterial ischemic stroke can be divided into emboli of cardiac and extra-cardiac origin, thrombosis due to disturbed homeostasis and disorders of cerebral arteries. NAIS uniquely involves not just the neonate, but maternal, obstetrical, placental, and also fetal factors. Several potential risk factors have been proposed, but definitive causative mechanisms have not been established. Often no single risk factor can be identified; multiple mechanisms likely co-exist and contribute to a stroke in an individual newborn.

The role of placental embolism in NAIS has gained increasing support[9]. Placental pathologies can be divided into infectious, inflammatory, and thrombotic disorders on the fetal side of the placental circulation[10-12]. The role of the placenta is further supported by the common occurrence of bilateral lesions, suggesting a proximal embolic source in the absence of cardiac pathology, and the extremely low risk of recurrence[13]. Though often difficult to obtain, the placenta and attached umbilical cord should be sent for pathological examination whenever possible as they may provide clues to stroke etiology in individual NAIS patients.

Currently, only in a minority of NAIS cases, a causative factor can be identified. Complex congenital heart disease and bacterial meningitis are well-established causes of NAIS with methods of definitive diagnosis. Prothrombotic factors are also commonly considered due to the evolutionarily adaptive mechanisms in coagulation systems that occur

during the birth process and in the early postnatal period[5,14,15]. Although genetic prothrombotic disorders may contribute to an increased risk of perinatal ischemic stroke the evidence for direct association is relatively weak[4]. A single-centre prospective population-based case-controlled study encompassing 212 neonates with perinatal stroke and 77 controls showed that thrombophilia in children with perinatal stroke is rare, with rates similar to the normal population[16]. The authors concluded that although disordered coagulation could contribute to the stroke, thrombophilia evaluation later in childhood is not indicated. A retrospective study of 215 infants with perinatal stroke concluded that even if present, neither thrombophilia, arteriopathy nor cardioembolic risk factors were predictive of recurrent perinatal stroke[4]. The extremely low recurrence rate after perinatal arterial ischemic stroke supports the role of mechanisms present only pre- or perinatally[3,4].

A recent controlled study demonstrated unique inflammatory profiles in babies with NAIS as compared to fetal strokes and controls[18]. Many additional clinical and laboratory factors have been examined for possible associations with NAIS, however, the correlations have been weak at best, often based on case reports or small case series. There is no evidence that mechanical factors or "birth trauma" can cause NAIS. Non-specific factors of fetal distress surrounding delivery including fetal heart rate abnormalities, presence of meconium, assisted delivery, low APGAR scores, and others have also been suggested in association with NAIS. More recently, Srivastava et al.[19] identified several prenatal factors that have a reasonable predictive value in identifying fetal risk for stroke. These included maternal age, tobacco exposure, recreational drug exposure, preeclampsia, chorioamnionitis, intrapartum maternal fever, emergency cesarean delivery, low 5-minute Apgar score, and male sex. Though these factors do not identify a biological marker for stroke mechanism, they probably reflect the fetal distress or factors leading to distress, affiliated with another more likely causative mechanism such as infection, systemic disease, placental pathology, or difficult labour.

DIAGNOSIS

Diagnosis of NAIS is usually made after a term newborn presents acutely with seizures or encephalopathy, leading to urgent neuroimaging and revealing an acute ischemic stroke in the arterial territory. Seizures are the presenting or predominant symptom in almost 90% of neonates with NAIS. Seizure onset 12 hours or more after birth and, specifically, the presence of focal motor seizures are independent predictors of stroke[20].

The middle cerebral artery, MCA, is a large-vessel artery that is most often affected (Figure 1a).

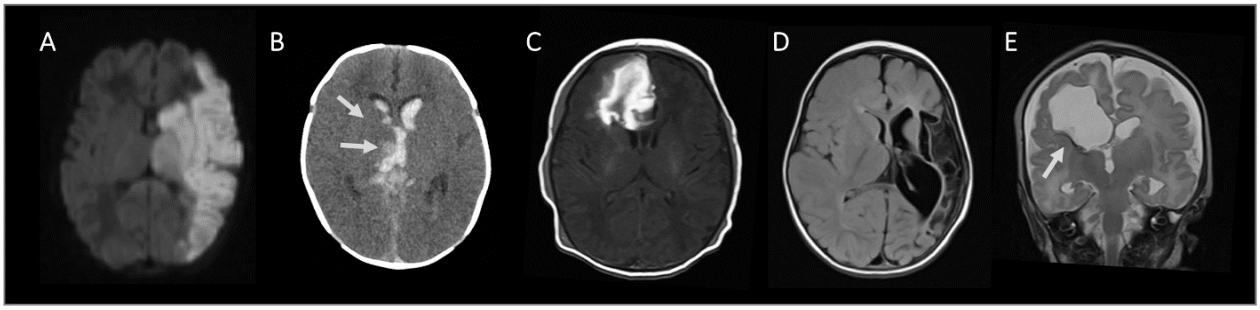

Figure 1. Perinatal stroke imaging. (A) Neonatal arterial ischemic stroke (NAIS) as seen on axial diffusion weighted imaging (DWI). **(B)** CT shows intraventricular hemorrhage in a term baby due to deep CSVT. Note primary hemorrhagic infarct in right thalamus (arrow) and edema in basal ganglia (top arrow). (C) Neonatal hemorrhagic stroke (NHS) as seen on axial T1-weighted sequence. **(D)** Arterial presumed perinatal ischemic stroke (APPIS) with focal encephalomalacia in left MCA territory seen on axial FLAIR. **(E)** Periventricular venous infarction (PVI) as seen on coronal T2-weighted sequence. Note remote blood product in subventricular zone (arrow).

Hemiparesis is not a common presenting symptom, due partly to the persistent bilateral cortical connections in the newborn. Subtle hemiparesis in a newborn can present as a mild asymmetry of primitive reflexes, specifically Moro or tonic neck reflex, which can be difficult to recognize even by experienced neonatal intensive care staff. Strokes affecting parietal and occipital lobes would cause sensory deficits which are difficult to recognize in a newborn. Diencephalic injury may result in disturbed temperature control, poor feeding, lethargy, and abnormalities of the sleep-wake cycle.

A common approach to neonatal encephalopathy and neonatal seizures in most centers includes brain imaging leading to a timely diagnosis of stroke[17]. Consensus-based imaging protocols have been developed to facilitate accurate and timely diagnosis of neonates with suspected stroke[21]. Magnetic resonance imaging (MRI) is the neuroimaging test of choice, since it lacks radiation exposure, and has superior anatomic resolution and sensitivity for acute ischemia. However, even with the improving sensitivity of MRI, early findings could be subtle and easily missed[17]. Core recommended sequences include diffusion-weighted imaging and apparent diffusion coefficient mapping to diagnose acute ischemia, gradient-recalled echo or susceptibility-weighted imaging to detect intracranial blood and its breakdown products, and T1- and T2-weighted imaging to assess for myelination, extra-axial blood and edema[21]. In neonates, the full extent of the infarction on DWI imaging can be underestimated during the first 24 hours and again after day five of the brain injury. From day seven onward, fluid-attenuated inversion recovery (FLAIR) MRI sequences are more reliable than DWI[5]. Experts believe that traumatic vascular injury and congenital vessel anomalies are likely underdiagnosed and will be missed unless intracranial and cervical vessel imaging is included in the evaluation[5]. Therefore, in our centre, we add magnetic resonance angiography (MRA) to assess for vascular abnormalities, and magnetic

resonance venography (MRV), especially if there is a suspicion of venous thrombosis (Figure Protocols).

ACUTE NEONATAL STROKE SAMPLE PROTOCOL

Arterial Ischemic Stroke (NAIS)	Cerebral Sinovenous Thrombosis (CSVT)	Hemorrhagic Stroke (NHS)

Signs indicating potential stroke

- Seizures
- Altered Mental Status
- Abnormal Tone
- Focal Signs
- Apnea
- Acute neurological deterioration

↓

Imaging: Neonatal MR Protocol *(Sequences: DWI/ADC, GRE/SWI, T1, T2, MRA, MRV)*

Consider TOF MRA Neck: to exclude carotid dissection

If MRI not available or contraindicated:

CT head +/- CTA or CTV

Cranial US

↓

Neuroprotective Care

Maintain Normothermia, normovolemia, normoglycemia

Avoid direct pressure over occiput (especially in CSVT)

Consider continuous video EEG (or aEEG if conventional continuous EEG is not available)

Treat seizures, clinical and electrographic

↓

(Continued in next page…)

NOTIFY NEUROCRITCAL CARE TEAM		
Arterial Ischemic Stroke (NAIS)	Cerebral Sinovenous Thrombosis (CSVT)	Hemorrhagic Stroke (NHS)
Stroke-specific investigations		
Cardiac Echo Placental pathology		Coagulation work up (CBC, PTT/INR)
Stroke-specific Management		
Consider anticoagulation (ACT) if ongoing risk of cardiac embolism	Initiate anticoagulation unless contraindicated*	Neurosurgery consult
Additional Imaging		
Usually not indicated Consider, if original study incomplete, or unexpected concerns	MR/MRV + GRE/SWI in 5-7 days if no ACT to exclude propagations. Otherwise in 6 weeks if ACT and stable	MR/MRV + GRE/SWI In 6-12 weeks or PRN

Determine the need for coagulation testing

Any of the following present:

- Confirmed CVST

OR

- Strong family hx of thrombotic disease

OR

- Multiple thrombosis sites

OR

- Large burden of thrombosis

Coagulation Testing will be determined by Hematology:

- Newborn: Prot C, S and antithrombin, PT/PTT
- (Factor V Leiden and Prothrombin G20210A at 3 mo of age)
- Maternal testing: ANA, Lupus, Anticardiolipin Ab, Homocysteine
- Both parents: Prot S and C

Family Education

Review evidence-based outcome

Provide Parent Guide to Pediatric Stroke, web-based resources (IPSO, IAPS)

Follow up

Neurocritical Care phone follow-up 2 weeks after discharge

Refer to perinatal stroke clinic (4-6 weeks for CSVT)

Provide contact information

(stroke neurologist, Neurocritical NP phone #, pediatric neurology nursing phone #)

MRI is not always feasible, particularly in critically ill neonates, due to the need for transportation to the radiology suite and prolonged scanning time. Cranial ultrasonography can be easily done at the bedside but while it can detect intraventricular hemorrhage, it is much less useful for detecting ischemic strokes, often localized more peripherally[22,23]. Head CT can serve a similar purpose when MRI is not readily available and acute intracranial pathology such as bleeding needs to be excluded. Here it should be recognized that CT scans may not show evidence of injury in the first 24 hours, though the more severe the infarct, the more likely it will be visible. Follow-up neuroimaging with MRI should be done whenever possible.

MANAGEMENT

Once stroke in a newborn is diagnosed, the main focus should be directed at the identification and treatment (if available) of underlying conditions and avoiding exacerbation of an existing injury. Supportive measures include neuroprotection, seizure control, adequate oxygenation, correction of dehydration and anemia, and monitoring and correction of metabolic disturbances, including acidosis, hypoglycemia, hypocalcemia, and electrolyte disorders[5].

Prompt investigations to initiate specific treatments are required although most NAIS cases will not require intervention beyond the above neuroprotective strategies. Bacterial meningitis may cause both perforating and large vessel vasculitis with ongoing stroke recurrence risk, prompting some to consider a course of corticosteroids for which a favourable safety profile already exists[26-28]. A neonate with an abnormal cardiac examination should undergo prompt echocardiography which may reveal a high recurrence risk and consideration of anticoagulation. The utilization of aspirin (5 mg/kg/day) has been variably used at different institutions, but only in a minority, and is largely empiric as strong evidence for anti-platelet or anti-coagulant treatment does not currently exist.

Seizures are an independent risk factor for worse outcomes in neonates with acute brain injury and therefore should be promptly treated. Experimental and clinical studies have conclusively shown that neonatal seizures on an already injured brain worsen the injury. Our laboratory showed that kainic acid-induced seizures superimposed on even a mild hypoxic-ischemic injury will further brain injury[29]. Glass and Miller substantiated these findings in newborn infants[30] as have others. Clinical identification of seizures in neonates can be difficult even for the most experienced observers. Therefore, continuous neuromonitoring with video electroencephalography (EEG), or at least simplified amplitude-integrated EEG[31] may be necessary to accurately characterize seizure burden and direct treatment. Diagnosing seizures in neonates with acute stroke on a clinical basis only increases the risk of both under and overdiagnosis of seizures. Furthermore, treatment with antiepileptic medications can lead to electroclinical uncoupling, resulting only in electrographic seizures. Therefore, neuromonitoring using

continuous EEG or amplitude-integrated EEG should ideally continue until no electrographic seizures are detected for 24 hours. There is no stroke-specific evidence regarding the choice of antiseizure medication but recent trials in related hypoxic-ischemic encephalopathy (HIE) populations suggest phenobarbital may be superior to levetiracetam[32]. The natural history of acute stroke-related seizures in the neonate is a resolution within 72 hours, suggesting most infants do not require ongoing treatment with antiseizure medicines following discharge. Current recommendations suggest the discontinuation of anti-epileptic medication following a normal EEG at 7 days of age or at discharge[33].

Thrombophilia testing has limited clinical value in the absence positive family history or additional thrombotic complications[4,16]. It must be interpreted with caution since levels of protein C, protein S and antithrombin are physiologically decreased to 30% of adult values and reach normal values only later in childhood, therefore repeated confirmatory testing or further genetic testing is often required to confirm the diagnosis[5,16,34]. Moreover, many of the thrombophilia factors act as acute phase reactants and will be falsely elevated, requiring the tests to be repeated later in childhood. Methylene tetrahydrofolate reductase C677T is no longer recommended[5,34]. We suggest thrombophilia testing only in rare circumstances when there is a compelling family history and if there are other signs or symptoms of an underlying prothrombotic disorder, such as the presence of clots, unexplained bleeding, or bruising.

In the absence of underlying thrombophilia, a cardioembolic source or complex congenital heart disease, most perinatal thromboembolic strokes do not progress, and the risk of stroke recurrence is very low. Only in those selective cases with an increased risk for recurrence, treatment with antiplatelet therapy (aspirin) or anticoagulation (low molecular weight heparin – LMWH, or unfractionated heparin) is warranted. Hyperacute therapies, such as thrombolysis or mechanical thrombectomy, currently don't have a role in NAIS since the precise timing of the stroke is rarely known and the endovascular devices are not compatible with the small arteries of neonates[5].

The role of arteriopathy in perinatal ischemic stroke is unknown, but experts suggest that the prevalence is likely underestimated since neurovascular imaging is not routinely performed. A single-center retrospective study identified arterial findings in 35% of neonates with AIS for whom MRA was available. Low Apgar scores and the presence of sepsis were significantly more common in neonates with MRA findings[28].

In older children, evidence-based institutional protocols and the establishment of pediatric stroke centers have been shown to improve the diagnosis, management, and outcome of childhood arterial ischemic stroke. Although there are no similar studies on perinatal stroke, the availability of stroke expertise in the neonatal intensive care unit (NICU) and the development of evidence-based institutional guidelines, could similarly improve the diagnosis and management of stroke in newborns. While there are no strong

evidence-based protocols for the acute management of neonates with stroke, an example of our institutional approach is shown in Figure 2.

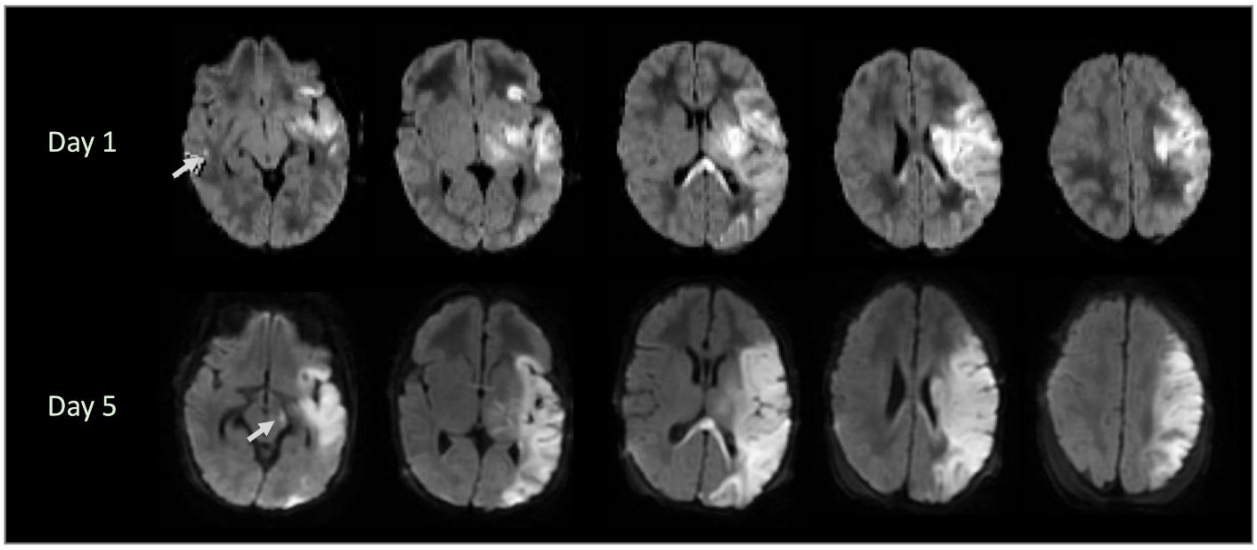

Figure 2. Evolution of NAIS injury. Diffusion MRI on day 1 shows a recent left MCA NAIS. Note small infarct in right hemisphere confirming proximal embolism (arrow). Repeat MRI at 5 days shows marked increase in stroke size (see left temporal lobe, 2nd images from left for example). Corticospinal preWallerian degeneration (diaschisis) is now evident (arrow).

ARTERIAL PRESUMED PERINATAL ISCHEMIC STROKE

Many perinatal stroke disorders will present outside the neonatal period. The most common presentation is an early hand preference, or other asymmetries of motor development, typically recognized by the parents at 4-6 months[3]. There may often be a delay of 6-12 months and several referrals before an MRI ultimately reveals the underlying stroke diagnosis[36]. Indeed, our own experience suggests that many children and possibly adults in the community with hemiparesis have gone undiagnosed since virtually the only cause for hemiparesis in an infant/child is a neonatal stroke.

In many cases, the MRI will reveal a chronic arterial infarct with well-circumscribed cystic encephalomalacia confirming an arterial territory, most often the MCA (Figure 1D). Such arterial presumed perinatal ischemic stroke (APPIS) occurs in approximately 1:7800 live births[6]. Such lesions are indistinguishable from chronic NAIS injuries since these likely represent the same disease, differing only in the timing of presentation (i.e., seizures did not occur or were unrecognized in the neonatal period). The presentation as hemiparetic CP dictates a selection bias towards APPIS lesions that affect the motor system though other presentations may be recognized later in childhood. These include visual field deficits or remote symptomatic epilepsy. Similarly, presumed perinatal hemorrhagic stroke (PPHS) has also been described but appears to be very rare[37].

While most perinatal strokes present in the neonatal period, certain stroke syndromes such as presumed perinatal arterial ischemic stroke or periventricular venous infarction are diagnosed in late infancy or even in childhood. Presumed perinatal arterial ischemic stroke (PPAIS) can be considered a delayed presentation of NAIS, where a stroke diagnosis is made retrospectively. The terminology 'presumed' is used given the clinical presentation of focal neurologic deficits present from early on in infancy, with no other acute injuries identified that could account for the injury.

DIAGNOSIS

Seizures, hemiparesis or focal motor dysfunction can be first detected in infants older than 28 days of life after a normal neonatal course[3]. Diagnosis of presumed perinatal arterial ischemic stroke is made after neuroimaging reveals focal remote injury or encephalomalacia in an arterial distribution. The diagnosis is based on the neuroimaging findings in the setting of otherwise essentially normal birth, and no inciting events during the child's life that could account for the brain injury (hence presumed).

PERIVENTRICULAR VENOUS INFARCTION

The most common presumed perinatal stroke disorder is periventricular venous infarction (PVI) with a birth prevalence of approximately 1:6000 live births[6]. Long recognized as a common lesion in hemiparetic CP populations, the mechanism of PVI has only been appreciated in recent years thanks to advanced imaging. PVI occurs in the fetus where germinal matrix hemorrhage (presumably before 32 weeks gestation) leads to secondary infarction of the periventricular white matter[3,38]. The resulting lesion is distinguishable from arterial strokes on MRI. First, they do not occur in a specific arterial supply region. Secondly, the lesions are that of focal encephalomalacia limited to the periventricular white matter with sparing of the cortex and deep grey matter and, often, evidence of residual subependymal blood on susceptibility weighted imaging sequences[36]. (Figure 1).

Most children with PVI will have injuries to the corticospinal tracts, based on the location of their injuries. Although cortical structural changes may be seen above PVI lesions[39] most children will have pure motor deficits. Seizures are rare[3]. Mutations in COL4A1 can create PVI-like lesions and genetic testing should be considered when bilateral lesions or positive family history are present.

PATHOPHYSIOLOGY

Though periventricular venous infarction (PVI) pathogenesis also relates to a hemorrhagic injury with secondary focal infarction, it is not associated with a difficult transition from fetal to postnatal life[40]. This is because the hemorrhage in PVI occurs in utero and is thus typically not symptomatic in the perinatal period. Small studies have suggested the role of some chronic maternal factors in PVI etiology such as hypertension, antepartum bleeding, and antepartum infection[40] though confirmatory studies are needed. The distribution of the lesions appears to be predominantly at the confluence of veins near the outer angles of the lateral ventricle and

the caudothalamic groove. These regions are prone to hemorrhage based on the immaturity of the vessel walls, and the combination of sluggish venous outflow together with the 'sharp' angles of the venous outflow tracks at these junctures (Figure 1) [42]. Recent data from the Canadian CP Registry suggests there is no association with perinatal factors as would be expected given the timing of the stroke months before birth[41].

DIAGNOSIS

Since PVI is a deep white matter injury (Figure 2b), it is less likely to present with seizures compared to the other perinatal stroke syndromes. It generally is identified only later in life once hemiparesis becomes apparent in an infant or child. PVI may present similarly to PPAIS as seizure or upper limb hemiparesis; however, it often uniquely involves weakness of the lower limb based on the orientation and neuroanatomical course of the corticospinal motor tracts.

OUTCOME

Most survivors of perinatal stroke have lifelong morbidity. Motor deficits, most commonly spastic hemiplegic cerebral palsy, predominate, but cognitive, and behavioural disorders and epilepsy are common[17]. The extent of neurodevelopmental impairment depends on the developmental timing of the injury (i.e., age of gestation), size and location of the injury (cortical, subcortical, or both), as well as whether cortical structures, subcortical structures or both are involved.

Perinatal arterial ischemic stroke is the most common type of perinatal stroke, therefore the most outcome data come from follow-up studies of arterial ischemic stroke. Approximately one-third of infants with perinatal ischemic stroke have a normal outcome[54-56]. Thrombophilia, arteriopathy and cardioembolic risk factors do not predict recurrence[4].

Abnormal findings on neurological examination at discharge, neonatal seizures and need for rehabilitation predict abnormal outcomes[55,56]. The most common disabilities include impaired language, cerebral palsy, intellectual disabilities, vision problems, learning disabilities and epilepsy[56]. In survivors with abnormal outcomes, multiple comorbidities are present in at least half[55,57] although the prevalence of severe disabilities is low[56]. Perinatal arterial ischemic stroke is the major cause of cerebral palsy accounting for approximately a third of hemiplegic cerebral palsy[4] and over 90% of all children with hemiplegic cerebral palsy. The development of cerebral palsy is more likely with larger stroke, corticospinal tract involvement and delayed clinical presentation[4,59] In some children, neuromotor impairment can become obvious only later at school age. The site of laterality of the vascular distribution does not seem to correlate with the long-term outcome[55].

Approximately 25% of children with unilateral stroke develop cognitive impairment, and the risk is much higher with bilateral infarction. A stroke affecting cortical and subcortical regions, specifically basal ganglia and thalamus, and the presence of acute seizures have been associated with reduced cognitive abilities in pediatric stroke survivors at 12

months post brain injury[60]. While the prognosis of motor development is based on early neuroimaging, predictors for the cognitive outcome are less well established[61]. Intellectual impairment and learning disabilities might not become apparent until school age, when impaired non-verbal reasoning, working memory and processing speed become apparent. A recent retrospective cohort study found that aEEG and NIRS values were associated with neurocognitive development at 15 to 24 months of age even after correction for the size of the lesion[61]. Epilepsy is also associated with worse cognitive outcomes[62].

Studies on the effects of perinatal stroke on vision are limited. Affected children will have significant variability in deficits based on location and extent of the injury, as approximately 8-16 % of perinatal strokes occur in the posterior cerebral artery (PCA) territory[63].

As part of a review which included 136 children with perinatal stroke, the most common visual abnormality was visual field defects[64]. In most cases, visual acuity was either normal or not reported with only 1 case of a documented visual acuity deficit. Other visual deficits included "blindsight" (perception of visual stimuli without functional vision; four children); visual cancellation errors (38 children); orthoptic eye movement abnormalities (seven children); optokinetic nystagmus (three children); hemispace bias (23 children); and crowding acuity (two children) deficits[64].

Epilepsy is a common consequence of perinatal stroke, but the exact prevalence and risk factors other than neonatal seizures are unknown. Remote seizures and the development of remote symptomatic epilepsy including medically refractory epilepsy are common after perinatal stroke[65,66]. Epilepsy can become refractory in approximately 25% of perinatal stroke survivors. Intuitively, patients with focal perinatal stroke lesions could make excellent surgical candidates. Surgical intervention is often complicated by seizure foci being widespread and rarely limited to the area of injury identified through neuroimaging, often requiring invasive monitoring[67]. Despite that, perinatal stroke survivors with medically refractory epilepsy might benefit from an early consideration of epilepsy surgery, since long-term functional outcomes have been good, including improvement in cognitive development and motor skills[67]. Early hemispherectomy for refractory seizures including infantile spasms has also been associated with improved cognitive outcomes[68,69]. Electrical status epilepticus has been described in children with perinatal stroke, leading to the development of sleep-related epileptic encephalopathy[70]. Disruptions of the thalamic oscillating rhythms seen in sleep due to the early developmental insult disrupting the normal maturation of neuronal networks might be the pathophysiological mechanism[71]. Based on our experience we suggest obtaining sleep-deprived EEG in children with a history of perinatal stroke who demonstrate regression or plateauing in their development, or behavioural changes, at any age, to rule out sleep-related epileptic encephalopathy[70].

Although most infants presenting with presumed perinatal stroke will develop hemiplegic CP, this is true for only about half of the infants with acute symptomatic strokes.

FAMILY AND PATIENT SUPPORT:

Parental morbidity is a substantial but under-investigated consequence of perinatal stroke. Studies on perinatal stroke pathobiology and outcome are increasing, but the process of adaption to the diagnosis and the long-term impact on caregivers' and families' function and wellbeing has been largely unknown[72]. Perinatal stroke impacts the child, parents and caregivers across complex aspects of life and over the child's lifespan, but there are only very few studies evaluating the well-being of caregivers of children with perinatal stroke[73]. Studies on parents and caregivers of children with chronic neurological conditions including cerebral palsy, epilepsy, and neurodevelopmental disabilities, highlighted that although most parents demonstrate resiliency, they are still at an increased risk for psychological concerns. Increased rates of stress, depression and other mental health concerns have been consistently found among caregivers of children with cerebral palsy[74]. Caregivers' quality of life is influenced by the condition severity, caregivers' psychological functioning as well as other aspects of their well-being including their health, relationships, independence, beliefs and environment[75]. Gender differences in how female and male caregivers perceive and cope with stress coping have also been observed[76]. Mothers of children with mild sequelae of perinatal stroke have been shown to adapt very well. In contrast, mothers of children with moderate and severe disabilities following perinatal stroke, tend to have an increased risk of depression, decreased marital satisfaction, poorer health-related quality of life and poorer family functioning, reflecting the need for additional resources and services[73]. A very important finding, and a target for intervention, is a greater burden of guilt and anxiety regarding their child's condition, explained by authors as likely due to the exceptionally intimate involvement with their child at the time of stroke, in utero or around birth as well as largely unknown pathophysiology of perinatal stroke, leaving them with the questioning of their actions before and around the delivery[72]. Therefore, the influence of medical professionals, therapists and support workers who assist families affected by perinatal stroke should seek to reduce the caregiver's blame and guilt which could be done through psychoeducation[73].

Focused family supports for this unique population can identify caregivers at risk for psychological concerns, including parental depression, marital satisfaction, family functioning and health-related quality of life[73]. Such support will benefit the entire family since parental well-being has been consistently shown to have a positive impact on the health and psychological functioning of children with disabilities[77,78]. Family-centred care promotes the psychological well-being of caregivers and children has been associated with greater satisfaction with services. The role of the child's stroke rehabilitation team is to develop a long-term plan that can be updated as the child progresses and improves. Caregivers benefit from training on how to help their children

during rehabilitation. Online resources are increasingly available for families through national and international pediatric stroke associations. With increased recognition of stroke in children, support organizations have been created to provide educational resources for children, caregivers, the community, and healthcare professionals.

Comprehensive pediatric stroke programs have emerged in many centres, providing children and their families affected by cerebrovascular diseases with prompt diagnosis, state-of-the-art treatment, and rehabilitation, as well as ongoing support. Many such centres also provide opportunities to participate in clinical research.

Many caregivers find it helpful to talk to other families affected by perinatal stroke through family support groups. Family support groups are made of individuals who understand what it is to be a caregiver to a child with a stroke, and often can help with their own experience. The child's healthcare or rehabilitation team often knows about support groups in the area and can help to make a contact with the group[79].

FUTURE DIRECTIONS:

There are many pressing issues in perinatal stroke. Without a better understanding of perinatal stroke pathophysiology, preventative strategies cannot effectively be developed[17]. While early neuroimaging is a gold standard for the diagnosis of perinatal stroke and it can help predict motor outcomes, the role of neuroimaging in the prediction of cognitive outcomes is less clear[61]. Once methods are developed for early neurodevelopmental prognostication, early intervention strategies for neuroprotection and neuroregeneration can be initiated.

The role of the placenta in perinatal arterial ischemic stroke is supported by small pathological and clinical studies. The risk of recurrence is close to zero providing further evidence of mechanisms unique to a pregnancy and perinatal period. However, proving it is exceedingly difficult because strokes are diagnosed within days after birth when the placenta is no longer available for analysis. Large-scale placental tissue-banking studies are needed, in conjunction with neonatal and maternal biomarker profiles to potentially identify at-risk pregnancies and develop prevention strategies[17].

Therapeutic hypothermia has well-established benefits in neonatal hypoxic-ischemic encephalopathy, but whether it has any potential neuroprotective role in neonatal arterial ischemic stroke is not clear. The first preclinical study of therapeutic hypothermia in an animal model of neonatal arterial ischemic stroke suggested its positive impact, as determined by functional and structural brain assessment and an improvement in motor behaviour. However, neonatal strokes are diagnosed within days of birth, far from the established therapeutic hypothermia window of 6 hours after birth. Future studies will be needed to explore the neuroprotective role of therapeutic hypothermia and especially its timing in neonatal arterial ischemic stroke[87]. Stroke-induced microglia activation and neuroinflammation have been proposed to play a role in the pathological progression of neonatal stroke. In an animal

model of a neonatal stroke, post-stroke administrations of aspirin, clopidogrel and coenzyme Q10 were shown to reduce infarction volume and increase motor function in experimental animals, suggesting a potential role for neuroprotection to be explored in the future[88]. Preclinical research and first clinical studies have shown promising neurodegenerative effects and the safety of growth factors and stem cells, making them potential candidates for novel treatment strategies to improve neurodevelopmental outcomes after perinatal arterial ischemic stroke[61].

Aside from differences in etiology and low risk of recurrence, perinatal stroke has different mechanisms for recovery compared to stroke in older children[83]. Stroke leads to secondary cell death and loss of function, which in the developing brain interacts with a complex process of brain maturation, including neuronal maturation, myelination, synaptogenesis, and normal neuronal pruning[90]. The consequence of stroke, resulting in degeneration and potential for regeneration likely varies with the stages of brain development as well as brain injury location and brain function[90,91]. While recovery from stroke in older children and adults occurs mainly through diaschisis reversal followed by functional adaptation through augmentation of complementary undamaged skills and neuroanatomical reorganization[89,95] in neonates, however; the main mechanism of stroke recovery appears to be a neuroanatomical reorganization, although the mechanisms are likely different compared to older children[91]. As a focal injury in an otherwise healthy brain, perinatal stroke presents an ideal human model of developmental plasticity by providing opportunities to study ongoing development after an early brain injury.

The role of co-morbidities is currently unknown, although neglect, visual field impairment and motor impairment likely limit cognitive development and the extent of what therapies can offer[89]. Therefore, the identification of both, targets that maximize plasticity and recovery, as well as the factors that might contribute to impairment, such as ongoing epileptic activity[70] might further improve our understanding of brain development.

Motor system plasticity has been a focus of intense clinical and preclinical research, and as a result, motor development after a unilateral perinatal injury is being increasingly better understood. A key element seems to be the degree of control of the hemiparetic side by the ipsilateral (contralesional) hemisphere. Corticospinal innervation is initially bilateral in newborns, and over time unnecessary ipsilateral projections degenerate, creating a mature corticospinal system with contralateral control. Injury in early life can change this normal development, leaving present increasing ipsilateral control and with that associated worse motor function. The goal now is to define new central targets that might be manipulated by the application of modulating approaches to improve function[17]. Early selection of patients at the greatest risk for impaired motor development would allow for early modulating therapies.

Routine clinical biomarkers of acute neonatal stroke that are predictive of hemiparesis might help to identify candidates for early rehabilitation[17]. Stroke volume assessed quantitatively on early DWI was shown to be strongly correlated with cerebral palsy at 2-year follow up which would allow for much earlier intervention. Some experts recommend combining neonatal brain MRI, neurological exam, and standardized general movement assessment (GMA) allowing for the diagnosis of CP in high-risk infants before 5 months of age. Abnormal GMA has a good positive predictive value, but normal GMA has to be interpreted with caution as the false positive rate is relatively high. Asymmetrical fidgety movements should be noticed because these could predict later mild unilateral cerebral palsy. Hand assessment for infants is another potentially useful indicator of mild cerebral palsy[92]. There are currently multiple trials focused on further enhancing motor skill gains by combining manual therapy with neurostimulation in children with perinatal stroke[93].

There are currently no standardized early interventions for children with perinatal stroke despite growing evidence for a critical time window of activity-dependent plasticity of the corticospinal tract development early in life[94]. The experts propose that targeted intervention during this unique period of plasticity could alter the consequences of the perinatal stroke to an extent not possible by intervention later in life. Transcranial magnetic stimulation has shown to be a feasible intervention to modulate motor learning in children after perinatal arterial ischemic stroke, but specific effects of location and timing need further research[97]. Combined repetitive transcranial magnetic stimulation (rTMS) and constraint-induced movement therapy (CIMT) have been shown to enhance therapy-induced functional motor gains in children with stroke-induced hemiparetic cerebral palsy, Class II evidence[94].

There may be potential for individualized rehabilitation based on measurable differences in plastic reorganization. However, the timing of the therapy is important because there might be a period in the early development when interventions might be of maximum benefit[17]. In addition, with a better understanding of how the brain reacts to injury, functional brain imaging may lead to personalized rehabilitation to optimize motor function based on the pattern of plastic adaptation seen in a particular child's brain[93].

Early prognosis of neurodevelopmental outcomes is important to inform the caregivers as well as to initiate neuroprotective strategies, but there are currently no established early predictors of neurodevelopmental outcomes[61]. Continuous neuromonitoring using amplitude-integrated EEG (aEEG) patterns and near-infra-red spectroscopy (NIRS) values are related to neurological outcomes in several neonatal disorders[99-101] although they are not standard of practice in perinatal stroke. In a recent retrospective cohort study on neonates with PAIS, slower recovery of a background pattern of ipsilateral aEEG and increased regional cerebral oxygen saturation (rScO2) asymmetry between cerebral hemispheres was related to an increased risk of cognitive

deficits at 18-24 months of age, even after correction for the size of infarction[61]. Continuous neuromonitoring could be a promising way to optimize the care of neonates with perinatal stroke, and it can be used even in neonates unstable for transport to MRI[61]. aEEG and NIRS could potentially be used to monitor the effects of early intervention, but first, more prospective research is necessary with a larger study population and more complete registration over several days[61].

From early neuroprotection to novel therapies improving physical constraints on learning, to early education targeting areas of a perinatal stroke child's strengths and weaknesses, there are many exciting possibilities for improving the care of children with perinatal stroke.

Corresponding author:

Jerome Y Yager

Faculty of Medicine & Dentistry -

Pediatrics Department,

University of Alberta, Edmonton, Canada

Email: jmailo@ualberta.ca

Funding:

None?

Conflicts of Interest:

None?

Acknowledgements:

None?

References:

1. Raju TNK, Nelson KB, Ferriero D, Lynch JK, NICHD-NINDS Perinatal Stroke Workshop Participants. Pediatrics. 2007 Sep;120(3):609-16. Doi:10.1542/peds.2007-0336

2. Dunbar M, Kirton A. Perinatal Stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury. Lancet Child Adolesc Health. 2018 Sep;2(9):666-676.

3. Kirton A, deVeber G, Pontigon AM, MacGregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol.* 2008;63(4):436-443.

4. Lehman L, Beaute BA, Kapur K, Danehy AR, Benson-Leung ME, Malkin BA, Rivkin MJ, Trenor CC III. Workup for perinatal stroke does not predict recurrence. Stroke. 2017; 48: 2078-2083.

5. Ferriero D, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, Meldau J, Roach ES, Smith ER on behalf of the American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Stroke. 2019 50:e51-e96.

6. Dunbar M, Mineyko A, Hill M, Hodge J, Floer A, Kirton A. Population Based Birth Prevalence of Disease-Specific Perinatal Stroke. Pediatrics. 2020 Nov;146(5):e2020013201.

7. Armstrong-Wells J, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Prevalence and predictors of perinatal hemorrhagic stroke: results from the kaiser pediatric stroke study. Pediatrics. 2009;123(3):823.

8. Grovaert. Prenatal Stroke. Semin Fetal Neonatal Med. 2009 Oct;14(5):250-66.

9. Srivastava R, Kirton A Perinatal Stroke: A Practical Approach to Diagnosis and Management. Neoreviews. 2021 Mar;22(3):e163-e176.

10. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, Ferriero DM, Fullerton HJ, Barkovich AJ, Wu YW. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA 2005 Feb 9;293(6):723-9.

11. Elbers J, Viero S, MacGregor D, DeVeber G, Moore AM. Placental pathology in neonatal stroke. Pedatrics. 2011:127:e722-e729.

12. Sorg Anna-Lisa, von Kries R, Klemme M, Gerstl L, Weinberger R, Beyerlein A, Lack N, Felderhoff-Musser U, Dzietko M. Risk factors for perinatal arterial ischemic stroke: a large case-control study. Developmental Medicine and Child Neurology 2020, 62: 513-520.

13. Mineyko A, Kirton A. The black box of perinatal ischemic stroke pathogenesis. *J Child Neurol.* 2011;26(9):1154-1162

14. Nelson KB, Lynch JK. Stroke in newborn infants. Lancet Neurol. 2004; 3:150-158.

15. Wu YW, Lynch JK, Nelson KB. Perinatal arterial stroke: understanding mechanisms and outcomes. Semin Neurol. 2005 Dec;25(4):424-34.

16. Curtis C, Mineyko A, Massicotte P, Leaker M, Jiang XY, Floer A, Kirton A. Thrombophilia risk is not increased in children after perinatal stroke. Blood. 2017 May 18;129(20):2793-2800.

17. Kirton A, deVeber G. Pediatric stroke: pressing issues and promising directions. Lancet Neurol. 2015; 14: 92-102

18. Mineyko A, Nettel-Aguirre A, de Jesus P, et al. Association of neonatal inflammatory markers and perinatal stroke subtypes. Neurology. Published online July 29, 2020. doi:10.1212/WNL.0000000000010309

19. Srivastava R, Dunbar M, Shevell M, Oskoui M, Basu A, Rivkin MJ, Shany E, de Vries LS, Dewey D, Letourneau N, Hill MD, Kirton A Development and Validation of a Prediction Model for Perinatal Arterial Ischemic Stroke in Term Neonates. JAMA Netw Open. 2022 Jun 1;5(6):e2219203.

20. Rafay MF, Pontigon AM, Chiang J, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. *Stroke*. 2009;40:58-64.

21. Lee S, Mirsky DM, Beslow LA, et al. Pathways for Neuroimaging of Neonatal Stroke. *Pediatr Neurol*. 2017;69:37-48.

22. Olivé G, Agut T, Echeverría-Palacio CM, Arca G, García-Alix A Usefulness of Cranial Ultrasound for Detecting Neonatal Middle Cerebral Artery Stroke. Ultrasound Med Biol. 2019 Mar;45(3):885-890.

23. Arca G, Arnaez J, Agut T, Núñez C, Stephan-Otto C, Valls A, García-Alix A. Neuron-specific enolase is correlated with lesion topology, relative infarct volume and outcome of symptomatic NAIS. Arch Dis Child Fetal Neonatal Ed. 2020 Mar;105(2):132-137.

24. Hernández MI, Sandoval CC, Tapia JL, Mesa T, Escobar R, Huete I, Wei XC, Kirton A. Stroke patterns in neonatal Group B streptococcal meningitis. A.Pediatr Neurol. 2011 Apr;44(4):282-8.

25. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. *Pediatrics*. 2020;145(6):e20193182. doi:10.1542/peds.2019-3182

26. Hernandez MI, Sandoval CC, Tapia JL, et al. Stroke patterns in neonatal group B streptococcal meningitis. *PediatrNeurol*. 2011;44:282-288. Neuron-specific enolase is correlated with lesion topology, relative infarct volume and outcome of symptomatic NAIS.

27. Dunbar M, Shah H, Shinde S, et al. Stroke in Pediatric Bacterial Meningitis: Population-Based Epidemiology. *Pediatr Neurol*. 2018;89:11-18.

28. Siddiq Ishita, Armstrong Derek, Surmava Ann-Marie, Dlamini N, MacGregor D, Moharir M, Askalan R. Utility od Neurovascular Imaging in Acute Neonatal Arterial Stroke. J Pediatr 2017; 188:110-4

29. Wirrell EC, Armstrong EA, Osman LD, Yager JY. Prolonged seizures exacerbate perinatal hypoxic-ischemic brain damage. Pediatr Res. 2001 Oct;50(4):445-54.

30. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. J Pediatr. 2009 Sep;155(3):318-23

31. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello J, Abend NS, Nguyen S, Wusthoff CJ, Clancy RR. The American Clinical

Neurophysiology Society's Guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011 Dec28(6):611-7. PMID 22146359.

32. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, Kuperman R, Harbert MJ, Michelson D, Joe P, Wang S, Rismanchi N, Le NM, Mower A, Kim J, Battin MR, Lane B, Honold J, Knodel E, Arnell K, Bridge R, Lee L, Ernstrom K, Raman R, Haas RH; NEOLEV2 INVESTIGATORS. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. Pediatrics. 2020 Jun;145(6):e20193182

33. Shellhaas RA, Wusthoff CJ, Numis AL, Chu CJ, Massey SL, Abend NS, Soul JS, Chang T, Lemmon ME, Thomas C, McNamara NA, Guillet R, Franck LS, Sturza J, McCulloch CE, Glass HC. Early-life epilepsy after acute symptomatic neonatal seizures: A prospective multicenter study.Epilepsia. 2021 Aug;62(8):1871-1882.

34. Monagle P, Barnes C, Ignjatovic V, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost*. 2006;95:362-372.

35. Kirton A, Deveber G, Pontigon AM, Macgregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. Ann Neurol. 2008 Apr;63(4):436-43.

36. Kirton A, Wei X. Teaching neuroimages: confirmation of prenatal periventricular venous infarction with susceptibility-weighted MRI. *Neurology*. 2010;74(12):e48

37. Cole L, Dewey D, Letourneau N, et al. Clinical characteristics, risk factors, and outcomes associated with neonatal hemorrhagic stroke: A population-based case-control study. *JAMA Pediatr*.

38. Takanashi J, Tada H, Barkovich AJ, Kohno Y. Magnetic resonance imaging confirms periventricular venous infarction in a term-born child with congenital hemiplegia. *Dev Med Child Neurol*. 2005;47:706-708.

39. Li D, Hodge J, Wei X-C, Kirton A. Reduced ipsilesional cortical volumes in fetal periventricular venous infarction. *Stroke*. 2012;43(5):1404-1407.

40. Kirton A, Shroff M, Pontigon AM, deVeber G. Risk factors and presentations of periventricular venous infarction vs arterial presumed perinatal ischemic stroke. *ArchNeurol*. 2010;67:842-848.

41. Vitagliano M, Dunbar M, Dyck Holzinger S, Letourneau N, Dewey D, Oskoui M, Shevell M, Kirton A.Perinatal arterial ischemic stroke and periventricular venous infarction in infants with unilateral cerebral palsy. Dev Med Child Neurol. 2022 Jan;64(1):56-62.

42. Raets M, Dudink J, Raybaud C, Ramenghi L, Lequin M, Govaert P. Brain vein disorders in newborn infants. Dev Med Child Neurol. 2015 Mar;57(3):229-40.

43. Ichord R. Cerebral Sinovenous Thrombosis. *Front Pediatr*. 2017;5:163.

44. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, David M, Humphreys P, Langevin P, MacDonald EA, Gillett J, Meaney B, Shevell M, Sinclair DB, Yager J; Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001 Aug 9;345(6):417-23.

45. Wu YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. *Ann Neurol.* 2003;54(0364-5134):123-126

46. Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. Arch Neurol. 2006 Mar;63(3):405-9.

47. de Veber; Yager JY, Black K, Bauman M, Massicotte P. Cerebral venous thrombosis in newborns, infants and children. Front Neurol Neurosci. 2008;23:122-31.

48. Jordan LC, Rafay M, Smith S, Askalan R,Zamel K, deVeber G, Ashwal S. Antithrombotic treatment in neonatal cerebral sinovenous thrombosis. Results of the International Pediatric Stroke Study. J Pediatr 2010; 156:704-10

49. Moharir MD, Shroff M, Stephens D, et al. Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study. *Ann Neurol.* 2010;67:590-599

50. Dunbar M, Kirton A.Semin Pediatr Neurol. 2019 Dec;32:100767.

51. Bruno CJ, Beslow LA, Witmer CM, et al. Haemorrhagic stroke in term and late preterm neonates. *ArchDisChild Fetal Neonatal Ed.* 2014;99:F48-F53.

52. Towner D, Castro MA, Eby-Wilkens E, Gilbert WM. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med.* 1999;341(23):1709-1714.

53. Brouwer MJ, de Vries LS, Pistorius L, Rademaker KJ, Groenendaal F, Benders MJNL. Ultrasound measurements of the lateral ventricles in neonates: why, how and when? A systematic review. *Acta Paediatr Oslo Nor 1992.* 2010;99(9):1298-1306.

54. deVeber G, Canadian Paediatric Ischemic Stroke Study Group. Canadian Paediatric Ischemic Stroke Registry: Analysis of children with arterial ischemic stroke. *Ann Neurol.* 2000;48(3):514.

55. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long- term outcome. *JPediatr.* 2000;137:351-355.

56. Chabrier S, Peyric E, Drutel L, et al. Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke. *J Pediatr.* 2016;172:156-161.e3. doi:10.1016/j.jpeds.2016.01.069

57. DeVeber G, MacGregor D, Friefeld S, Chan A, Meanery B, Domi T. Neurological Outcome in Survivors of Neonatal Arterial Ischemic Stroke. *Pediatr Res.* 2003;53(4):537A.

58. Lehman LL, Rivkin MJ. Perinatal Arterial Ischemic Stroke: Presentation, Risk Factors, Evaluation, and Outcome. *Pediatr Neurol.* 2014;51(6):760-768.

59. Wu YW, Lindan CE, Henning LH, et al. Neuroimaging abnormalities in infants with congenital hemiparesis. *Pediatr Neurol.* 2006;35(3):191-196

60. Anderson V, Darling S, Mackay M, Monagle P, Greenham M, Cooper A, Hunt RW, Hearps S, Gordon AL.Cognitive resilience following paediatric stroke: Biological and environmental predictors. Eur J Paediatr Neurol. 2020 Mar;25:52-58.

61. Wagenaar N, van den Berk DJM, Lemmers PMA, et al. Brain Activity and Cerebral Oxygenation After Perinatal Arterial Ischemic Stroke Are Associated With Neurodevelopment. 2019 *Stroke*.

62. van Buuren LM, van der Aa NE, Dekker HC, Vermeulen RJ, van Nieuwenhuizen O, van Schooneveld MM, de Vries LS. Cognitive outcome in childhood after unilateral perinatal brain injury. Dev Med Child Neurol. 2013 Oct;55(10):934-40.

63. Mercuri E, Anker S, Guzzetta A, et al. Neonatal cerebral infarction and visual function at school age. *ArchDisChild Fetal Neonatal Ed*. 2003;88(1359-2998):F487-F491.

64. Crawford LB, Golomb M. Childhood stroke and vision: A review of the literature. Pediatr Neurol. 2018. Apr;81:6-13.

65. Fox CK, Glass HC, Sidney S, Smith SE, Fullerton HJ. Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke. *Neurology*. 2016;86(23):2179-2186.

66. Rattani A, Lim J, Mistry AM, et al. Incidence of Epilepsy and Associated Risk Factors in Perinatal Ischemic Stroke Survivors. *Pediatr Neurol*. 2019;90:44-55.

67. Ghatan S, McGoldrick P, Palmese C, Le Vega-Talbott M, Kang H, Kokoszka AM, Goodman RR, Wolf SM. Surgical management of medically refractory epilepsy due to early childhood stroke. J Neurosurg Pediatr. 2014 Jul;14(1):58-67.

68. Wiebe S, Berg AT. Big epilepsy surgery for little people: what's the full story on hemispherectomy? Neurology. 2013 Jan 15;80(3):232-3.

69. Taussig D, Dorfmuller G, Save J, Fohlen M, Chipaux M, Ferrand-Sorbets S, Delalande O, Bulteau C. Hemispherectomy for isolated infantile spasms following perinatal ischemic stroke.

70. Mineyko A, Qi W, Carlson HL, Bello-Espinosa L, Brooks BL, Kirton A. Neuropsychological outcome in perinatal stroke associated with epileptiform discharges in sleep. *Can J Neurol Sci J Can Sci Neurol*. 2017;44(4):358-365.

71. Sánchez Fernández I, Takeoka M, Tas E, Peters JM, Prabhu SP, Stannard KM, Gregas M, Eksioglu Y, Rotenberg A, Riviello JJ Jr, Kothare SV, Loddenkemper T.Neurology. Early thalamic lesions in patients with sleep-potentiated epileptiform activity. 2012 May 29;78(22):1721-7.

72. Bemister TB, Brooks BL, Dyck RH, Kirton A. Parent and family impact of raising a child with perinatal stroke. *BMC Pediatr*. 2014;14:182.

73. Bemister TB, Brooks BL, Dyck RH, Kirton A. Predictors of caregiver depression and family functioning after perinatal stroke. *BMC Pediatr*. 2015;15:75.

74. Pousada M, Guillamon N, Hernandez-Encuentra E, Munoz E, Redolar D, Boixados M, Gomez-Zuniga Impact of caring for a child with cerebral palsy on the quality of life of parents: a systematic review of the literature. J Dev Phys Disabil 2013, 25(5):545-577

75. Terra VC, Cysneiros RM, Schwartzman JS, Teixeira MC, Arida RM, Cavalheiro EA, Scorza FA, de Albuquerque M.Mothers of children with cerebral palsy with or without epilepsy: a

quality of life perspective. Disabil Rehabil. 2011;33(5):384-8.

76. Matud MP, Bethencourt JM, Ibáñez I. Gender differences in psychological distress in Spain. Int J Soc Psychiatry. 2015 Sep;61(6):560-8.

77. Canary HE. Creating supportive connections: a decadeof research on support for families of children with disabilites. Health Commun. 2008 Sep;23(5):413-26.

78. Social support and adaptation outcomes in children and adolescents with cerebral palsy. Carona C, Moreira H, Silva N, Crespo C, Canavarro MC.Disabil Rehabil. 2014; 36(7):584-92.

79. Family Guide to Pediatric Stroke, 2014 www.heartandstroke.ca

80. Kirton A. Life After Perinatal Stroke. *Stroke*. 2013;44(11):3265-3271. doi:https://doi.org/10.1161/STROKEAHA.113.000739

81. Mineyko A, Kirton A. Long-Term Outcome After Bilateral Perinatal Arterial Ischemic Stroke. *Pediatr Neurol*. Published online August 2, 2019. doi:10.1016/j.pediatrneurol.2019.07.013

82. Hilderley AJ, Metzler MJ, Kirton A. Noninvasive Neuromodulation to Promote Motor Skill Gains After Perinatal Stroke. *Stroke*. Published online January 21, 2019:STROKEAHA118020477. doi:10.1161/STROKEAHA.118.020477

83. Murias K, Brooks B, Kirton A, Iaria G. A review of cognitive outcomes in children following perinatal stroke. *Dev Neuropsychol*. 2014;39(2):131-157. doi:10.1080/87565641.2013.870178

84. Mineyko A, Kirton A, Billinghurst L, et al. Seizures and Outcome One Year After Neonatal and Childhood Cerebral Sinovenous Thrombosis. *Pediatr Neurol*. 2020;105:21-26. doi:10.1016/j.pediatrneurol.2019.08.012

85. van der Aa NE, Dudink J, Benders MJ, et al. Neonatal posterior cerebral artery stroke: clinical presentation, MRI findings, and outcome. *Dev Med Child Neurol*. 2013;55:283-29

86. Gender and Psychological Well-Being. Matud MP, López-Curbelo M, Fortes D. Int J Environ Res Public Health. 2019 Sep 20;16(19):3531. doi: 10.3390/ijerph16193531. PMID: 31547223

87. Chevin M, Chabrier S, Dinomais M, Bedell BJ, Sébire G Benefits of hypothermia in neonatal arterial ischemic strokes: A preclinical study. Int J Dev Neurosci. 2020 Jun;80(4):257-266.

88. Yi YY, Shin HJ, Choi SG, Kang JW, Song HJ, Kim SK, Kim DW. Preventive Effects of Neuroprotective Agents in a Neonatal Rat of Photothrombotic Stroke Model..Int J Mol Sci. 2020 May 24;21(10):3703. doi: 10.3390/ijms21103703.PMID:

89. Murias K, Brooks B, Kirton A, Iaria G. A review of cognitive outcomes in children following perinatal stroke..Dev Neuropsychol. 2014;39(2):131-57.

90. Murias K, Moir A, Myers KA, Liu I, Wei XC.Systematic review of MRI findings in children with developmental delay or cognitive impairment. Brain Dev. 2017 Sep;39(8):644-655.

91. Kolb B, Teskey GC. Age, experience, injury, and the changing brain. Dev Psychobiol. 2012 Apr;54(3):311-25.

92. Pascal A, Govaert P, Ortibus E, Naulaers G, Lars A, Fjørtoft T, Oostra A, Zecic A, Cools F, Cloet E, Casaer A, Cornette L, Laroche S, Samijn B, Van den Broeck C. Motor outcome after perinatal stroke and early prediction of unilateral spastic cerebral Eur J Paediatr Neurol. 2020 Nov;29:54-61.

93. Hilderley AJ, Metzler MJ, Kirton A.Noninvasive Neuromodulation to Promote Motor Skill Gains After Perinatal Stroke. Stroke. 2019 Feb;50(2):233-239.

94. Kirton A, Andersen J, Herrero M, et al. Brain stimulation and constraint for perinatal stroke hemiparesis: The PLASTIC CHAMPS Trial. *Neurology*. 2016;86(18):1659-1667.

95. Nudo RJ. Neural bases of recovery after brain injury. J Commun Disord. 2011 Sep-Oct;44(5):515-20.

96. Pascal A, Govaert P, Ortibus E, Naulaers G, Lars A, Fjørtoft T, Oostra A, Zecic A, Cools F, Cloet E, Casaer A, Cornette L, Laroche S, Samijn B, Van den Broeck C. Motor outcome after perinatal stroke and early prediction of unilateral spastic cerebral palsy. Eur J Paediatr Neurol. 2020 Nov;29:54-61.

97. Hollis A, Zewdie E, Nettel-Aguirre A, et al. Transcranial Static Magnetic Field Stimulation of the Motor Cortex in Children. Front Neurosci. 2020;14:464.

98. Kirton A, Ciechanski P, Zewdie E, et al. Transcanial deirect Transcranial direct current stimulation for children with perinatal stroke and hemiparesis. Neurology. 2017;88(3):259-267.

99. Hellström-wa L, Rosén I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. Arch Dis Child Fetal Neonatal Ed. 1995 Jan;72(1):F34-8.
doi: 10.1136/fn.72.1.f34.PMID: 7743282

100. Toet MC, Flinterman A, Laar Iv, Vries JW, Bennink GB, Uiterwaal CS, Bel F. Cerebral Oxygen saturation and electrical brain activity before, during and up to 36 hours afetr arterial switch procedure in neonates withouot pre-exisiting brain damage: its relationship to neurodevelopmental outcome. Exp Brain Res. 2005 Sep;165(3):343-50.

101.Lemmers PM, Zwanenburg RJ, Benders MJ, de Vries LS, Groenendaal F, van Bel F, Toet MC.Cerebral oxygenation and brain activity after perinatal asphyxia: does hypothermia change their prognostic value? Pediatr Res. 2013 Aug;74(2):180-5.