**Perinatal Stroke**

The most focused lifetime risk for stroke is the week surrounding birth.1 A term newborn carries a risk of ischemic stroke of ≥1:3500, triple the weekly stroke risk of a smoking adult with diabetes mellitus and hypertension.1,2 Adding in populations of neonatal hemorrhagic stroke, sinovenous thrombosis, and late presenting presumed perinatal strokes likely more than doubles the incidence of perinatal stroke outcomes. How does a child develop new skills that his or her brain has never possessed during stroke recovery? How do we measure outcome as the child continues to grow into deficits with maturation? What are the modulators of developmental plasticity that might be targeted to achieve better functional outcomes? We review the current state of knowledge on perinatal stroke outcomes and attempt to highlight elements that might provide insight into these pressing questions.

**Perinatal Stroke Syndromes**

Advances in clinical research and neuroimaging have moved perinatal stroke from being a nondescript culprit in cerebral palsy to systematically classifiable, specific subtypes of focal brain injuries. These disease syndromes can be classified according to the following 3 simple variables: (1) When did the injury occur (before or near birth), (2) What was the mechanism (ischemic or hemorrhagic; arterial or venous), and (3) When was the child first symptomatic (acutely as a newborn or later in infancy). Combining careful interpretation of neuroimaging with clinical information to answer these questions reveals 5 distinct perinatal stroke syndromes (Figure).5,6 These distinct stroke subtypes all feature focal injury in an otherwise healthy brain. Collectively, they represent an ideal human model for the study of developmental plasticity and outcomes after focal early brain injury. They have both shared and different characteristics. Cortical, subcortical, and combined patterns of infarction are represented. Three subtypes have an arterial mechanism and 2 subtypes, cerebral sinovenous thrombosis (CSVT) and periventricular venous infarction (PVI), involve venous occlusion. PVI occur before 34 weeks gestation, whereas most arterial strokes occur close to term. This review will not discuss outcomes from vascular injuries in delivered preterm infants, although any of the 5 subtypes of perinatal stroke can occur preterm. The clinicoangiographic classification summarized in the Figure was developed based on best available understanding of the pathophysiology and built on a closely related consensus system.7 The separation of the 5 subtypes relies on characteristic neuroimaging features and seems to be both valid and relevant to clinical outcomes.5,7 However, such classifications are continually evolving, and different perinatal stroke terminologies also exist.

**Mechanisms of Recovery in the Developing Brain**

In the mature brain, changes after focal injury are complex but increasingly understood. In the immature brain, the complexity is compounded by neurodevelopmental aspects. This topic is elegantly discussed elsewhere8 but is briefly summarized here to provide a framework for understanding the discussion of outcomes that follow. Perinatal timing of acquired...
brain injury including stroke introduces multiple, often competing factors in brain maturation and development that will ultimately determine outcome. These include neuronal maturation and organization, myelination, pruning, and synaptogenesis. The relative impact of each of these processes on recovery varies depending on fundamental aspects of the injury, including timing and location.

Although mechanisms of recovery are far from clear, evidence supports the fundamental concept that outcomes from perinatal stroke differ from those of older children or adults with stroke. Essential components of adult stroke recovery include functional adaptation by augmentation of complementary, remaining skills and neuroanatomical reorganization.9 Although these factors are also relevant in perinatal brain injury, the immature brain is a highly dynamic system, resulting in different recovery mechanisms. Animal models demonstrate differences in gene expression, dendritic arborization, synaptic spine formation and density, and others in the immature compared with the mature brain.9

The historical Kennard principle suggested that younger brains have a greater capacity to recover from injury.10 More recently, the concept that the developing brain is actually more sensitive to injury has challenged this view. There is now substantial evidence from both animal and clinical studies to support this concept. Specifically, stroke during the perinatal time frame seems to carry a greater risk of adverse outcomes than stroke even in later infancy.11-13 It is also apparent that for different developing neurological functions there are different critical periods of susceptibility to disruption.10 Although stroke studies of children across pediatric ages have, to date, lacked the power to tease out the timing of these function-related susceptibility periods, the larger available samples of perinatal stroke subjects may offer insights into developmental plasticity from birth through childhood.

Outcomes From Perinatal Stroke

Outcomes from perinatal stroke are complex. Despite potential increased plasticity in the developing brain, most perinatal stroke survivors have lifelong neurological morbidity, at higher rates than similar lesions acquired in later infancy or childhood.13,14 Because speech and other higher cognitive functions emerge later in childhood, children with perinatal stroke are considered to grow into their deficits when specific developmental stages are reached.15 Long-term neuropsychological studies are now defining the evolution and spectrum of these higher order deficits. Because the Neonatal Arterial Ischemic Stroke (NAIS) syndrome dominates the published perinatal stroke literature, a categorical discussion of NAIS outcomes is provided, followed by succinct summaries of the remaining disease states.

Neonatal Arterial Ischemic Stroke (NAIS)

NAIS is the most common subtype of stroke presenting in the first week of life.16 Current estimates of incidence are ≈1:2500 to 3000 live births.17 Most present with focal seizures in the first days of life, usually without focal deficits or encephalopathy.17-19 Diffusion-weighted imaging confirms acute, focal brain infarction in an arterial territory (Figure). Most are large artery (typically left middle cerebral artery) occlusions with combined cortical and subcortical injuries and are multifocal in 20% to 30% of cases.19,20 Pathophysiology is poorly understood with most cases remaining idiopathic despite a lengthy list of possible risk factors, most of which lack solid evidence for a primary causative role.1

Motor

Hemiparetic cerebral palsy is often the result of perinatal stroke.17,21 However, motor deficits are relatively less common
in NAIS compared with the other perinatal stroke syndromes, with estimates of ≈25% to 50%.\textsuperscript{22,23} The upper extremity is most involved, reflecting the topography of the most common lesion, middle cerebral artery infarction. Motor deficits typically emerge in the first year, often when infants begin reaching and grasping at 4 to 6 months, and hand use asymmetry is noted. Unless they have bilateral infarcts, nearly all children will achieve independent walking by 14 months age.\textsuperscript{24} The motor deficits are dynamic during development, representing a complex integration of pure motor factors (weakness, tone/spasticity, orthopedic complications, etc) and childhood motor development, with additional influence of cognitive and behavioral factors, and others less understood (see below).

Despite the frequency and importance of motor deficits after perinatal stroke, evidence-based assessment and management of these are relatively poorly defined. Early initiation of multimodal rehabilitation therapy is generally considered beneficial.\textsuperscript{25} Such multidisciplinary teams would usually include physical, occupational, and speech therapists, orthopedic surgeons, pediatric physiatrists, and others. Consensus guidelines recommend muscle strengthening and ankle–foot orthoses for gait and contracture prevention.\textsuperscript{25} Botulinum toxin is increasingly used for treating focal spasticity or dystonia although studies specific to perinatal stroke are lacking.

As a focal injury of defined timing in a previously healthy brain, perinatal stroke represents an ideal human model for study. Recent advances have improved our understanding of motor development after perinatal stroke and identified novel central therapeutic targets potentially amenable to interventions. Combining animal studies with human neurophysiology and neuroimaging methods has generated new models of developmental motor plasticity.\textsuperscript{7} For example, excessive control of an affected upper extremity by the ipsilateral (non-lesioned) hemisphere after perinatal stroke seems to represent maladaptive developmental plasticity. Interventions that enhance motor control within the contralateral (lesioned) hemisphere might therefore be an informed approach to treatment. Evidence from randomized trials supports the efficacy of constraint induced movement therapy (CIMT) in congenital hemiparesis.\textsuperscript{26} Neuroimaging studies suggest CIMT involves enhanced motor control in the contralateral hemisphere.\textsuperscript{27} Noninvasive brain stimulation such as Transcranial Magnetic Stimulation (TMS) may further define the neurophysiology of recovery after perinatal stroke while providing the means to modulate the system toward improved function. Safety and tolerability of TMS in children is well established\textsuperscript{28a} but evidence of efficacy in perinatal stroke is lacking. Clinical trials evaluating these and other neuromodulation approaches in perinatal stroke are underway (http://clinicaltrials.gov, NCT01189058).

**Somatosensory**

Disordered sensation is likely an important contributor to disability but is virtually unstudied in perinatal stroke. Difficulty in accurately measuring sensory dysfunction in young infants and children has been a major barrier. Proprioception, the sensation of position, motion, and force, provides afferent input essential for integrated limb control. Studies of cerebral palsy populations have demonstrated errors in position-matching tasks suggestive of dysfunctional proprioception.\textsuperscript{28,29} In adult stroke, preservation of proprioceptive impacts recovery of upper extremity hemiparesis.\textsuperscript{30} Robotic technologies can now quantify proprioceptive functions in adult stroke\textsuperscript{31} as well as healthy children.\textsuperscript{32} Our preliminary robot data in children with perinatal stroke suggest that proprioception can be accurately measured, and is frequently severely impaired, particularly in those with arterial lesions (unpublished).

**Visuospatial**

Vision and visuospatial skills after perinatal stroke are not well studied. Deficits do occur after early brain injury and sometimes parallel the patterns of localization and lateralization established in adults.\textsuperscript{33} Measurement of visual perception in children requires complex testing. Existing evidence suggests that robust plasticity in visual cortex may allow many children to escape disabling hemianopias. However, specific mechanisms and functional significance of recovery are not well understood.\textsuperscript{14} As in adults, right hemisphere lesions are associated with impaired spatial integration (organizing elements into a unified whole), whereas left hemisphere injuries tend to impair processing detail.\textsuperscript{34} Using the block-design subtest of the Wechsler Intelligence Scale for Children (WISC), children with right hemisphere perinatal stroke had more global errors (overall design shape), whereas left-sided lesions made more local errors (precise internal pattern). Another recent study documented subtle visual and tactile neglect after perinatal stroke. Unlike adult stroke, left-sided lesions were often associated with neglect of bilateral stimuli with worse performance on the right. Similar to adults, right-sided strokes had difficulties with contralateral visual cancellation and manual exploration tasks.\textsuperscript{35}

**Cognition**

Neuropsychological morbidities including deficits in language, cognition, behavior, and other higher brain functions occur in up to 60% of children with arterial perinatal stroke.\textsuperscript{20,22} Numerous barriers to the study of neuropsychological outcomes in children with perinatal stroke exist. These include the complexities of the timing of appearance of specific deficits, a lack of consistent perinatal stroke subtype definitions, the use of variable outcome measures, and studies with modest sample sizes only rarely using a prospective longitudinal design.\textsuperscript{23,37}

Studies using standardized intelligence quotient (IQ) tests suggest that mean IQ levels are within the normal range.\textsuperscript{20,37,38} However, prospective longitudinal studies have also demonstrated specific disorders of cognitive function that become more apparent with time.\textsuperscript{15} Studies comparing matched controls are more likely to demonstrate specific differences.\textsuperscript{39} Most studies report a relative preservation of verbal versus performance abilities.\textsuperscript{12} Age at testing is critical because 1 study found near-normal IQ at preschool ages that shifted to significant deficits in the same children at school age.\textsuperscript{15} Marked inconsistency across small, averaged populations suggests the possibility that at-risk subpopulations may be harboring the
bulk of cognitive morbidity. Children with seizures may be particularly at risk (see below).

**Executive Function and Attention**

Executive functions include behavioral and emotional self-regulation (e.g., attention, inhibition, mental flexibility, working memory, and metacognitive skills such as planning and problem solving). These functions are not well studied after perinatal stroke. General cognitive evaluations have suggested a relative sparing of executive function. However, studies of congenital hemiplegia (including perinatal stroke) describe increased rates of attention disorders. There is also evidence that attention deficit hyperactivity disorder prevalence is increased after childhood stroke and is associated with earlier age at injury. Given the potential impact on other elements of development and available treatments, studies of attention disorders after perinatal stroke are urgently needed.

**Language**

Perhaps the most striking difference in lesion-specific outcomes between perinatal and adult stroke is language. Developmental language disorders occur in 20% to 25%, and these occur at similar rates with right or left hemisphere lesions. However, subtle lateralization features may be present. For example, school-age children with left hemisphere perinatal stroke seem to make more morphological errors, use less complex syntax, and produce less detailed story settings when relaying a personal narrative. Modestly powered functional magnetic resonance imaging studies suggest a spectrum of ipsilesional versus contralesional language organization with mixed correlations to expressive and receptive functions. One case–control study of language in 25 children with left hemisphere perinatal stroke found that both preservation of ipsilesional frontal areas and bilateral representations of temporal–parietal language areas were associated with normal function.

**Epilepsy**

Among perinatal strokes, children with arterial lesions carry the highest risk of epilepsy, although reported rates vary widely (15% to 54%). Despite a unilateral lesion, infantile spasms and other epileptic encephalopathies can occur. Fortunately, many children eventually outgrow their epilepsy. Treatment studies specific to perinatal stroke have not been completed, although they may be excellent epilepsy surgery candidates. The treatment of acute neonatal seizures in perinatal stroke is unstudied, but importantly, continuous electroencephalogram (EEG) monitoring often detects subclinical seizures. A link between early seizures and later epilepsy suggests a role for more aggressive EEG monitoring and treatment in neonatal stroke.

Accumulating evidence supports an association between seizures and adverse neuropsychological outcomes. In a longitudinal study, full scale intelligence quotient scores were near normal and steady with time. However, when populations with and without seizures were dichotomized, a strong association with abnormal IQ was noted. New data from our population-based perinatal stroke registry support an association with epilepsy and, in particular, sleep-related EEG abnormalities. Using blinded analysis of sleep EEG recordings, the presence of continuous discharges in slow wave sleep (CDSS) seems highly correlated with abnormal neuropsychological outcomes. All children with CDSS had severely abnormal outcomes, whereas only 12% of children without CDSS (including 53% with epilepsy) had severe deficits (unpublished). These preliminary findings suggest pathological EEG activity may be both a biomarker and potentially modifiable modifier of neuropsychological outcomes in perinatal stroke.

**Outcome Prediction**

Early prediction of long-term neurological outcome is important to families and facilitates patient selection for clinical trials. The ability of clinical, laboratory, and EEG measures to predict outcomes has been limited. Neuroimaging findings may be more predictive including lesion size and location. Diffusion magnetic resonance imaging markers of corticospinal tract Wallerian degeneration seem to predict adverse motor outcomes. Acute diffusion imaging may also demonstrate changes in connected brain structures, so-called diachisis or network injury, associated with outcome. Early diffusion tensor imaging may also assess functional tract integrity in NAIS with implications for long-term outcome prediction.

**Psychology, Mental Health, and Family-Centered Care**

The education, support, and counseling of the growing child and their family are essential and increasingly recognized. Developmental psychology research specific to perinatal stroke is surprisingly lacking despite abundant child psychology issues including physical disability, bullying, and suspected but unproven increases in anxiety and depression. Quality of life may be better than adult stroke overall, underestimated by parents, and inversely related to degree of cognitive dysfunction. Our early results suggest parental psychological outcomes are also frequently abnormal. Because a definitive cause cannot be identified usually, mothers may harbor unjustified feelings of guilt or blame. Connections to educational and support resources should be sought with expert-driven, best-practice documents now readily available. Families require access to information and an open channel of discussion to decipher an abundance of misinformation and make informed decisions. With survival for many decades, perinatal stroke morbidity lasts a lifetime, amplifying burden to individual, family, and society.

**Recurrence**

Recurrence of perinatal stroke is exceedingly rare, estimated at <1% for both the child and future pregnancies. An important exception exists in neonates with congenital heart disease who have a 14% risk of recurrent stroke. In other neonates, secondary stroke prevention is not usually required. With no established maternal risk factors, primary prevention strategies do not exist.
Neonatal Cerebral Sinovenous Thrombosis (NCSVT)

Although many children will not demonstrate focal brain infarction, outcomes from NCSVT are abnormal in most cases.56–58 In a systematically evaluated cohort of NCSVT (n=90) followed up for a median of 2.5 years, most (>60%) had neurological morbidity, with language and sensorimotor deficits being most common. Such a predominance of cognitive and neuropsychological deficits is consistent with previous literature56 and is remarkably evident considering the lengthy follow-up typically required to detect such problems. Motor deficits are less common compared with arterial perinatal stroke diseases but present in 20% to 50% and can often be severe with bilateral deep injuries.56,59,60 Predictors of poor outcome include neurological comorbidities and bilateral infarction.57,59 The risk of epilepsy after NCSVT is 15% to 40% and maximal in those with parenchymal infarction.56–59

Neonatal Hemorrhagic Stroke (NHS)

Long-term NHS outcome studies are limited. Collectively, they suggest an increased mortality but lower long-term morbidity compared with ischemic perinatal strokes. A single center study of 66 term neonates with intracranial hemorrhage (=50% extra-axial) assessed at a median of 3 years found a mortality of 13% but most survivors (57%) were neurologically normal.61 Another single center cohort study suggested similar outcomes in 53 term neonates with parenchymal hemorrhage and mortality of 25% but developmental delays in <20% and cerebral palsy in <10%.62 Typical of all perinatal brain injury outcome studies is the limitation imposed by relatively shorter term follow-ups with most children not reaching school-age where higher order deficits manifest. NHS recurrence risk seems to be low, perhaps suggesting that one-time pathogeneses such as small vascular malformations that rupture and obliterate during transition to extrauterine life account for a significant proportion of otherwise unexplained cases.

Arterial Presumed Perinatal Ischemic Stroke (APPIS)

Most PPIS cases are clear, wedge-shaped areas of encephalomalacia within an arterial territory, most often the middle cerebral artery (Figure D).5,63 In many cases, such lesions seem virtually indistinguishable from chronic imaging of symptomatic NAIS. Recent PPIS risk factor studies64 suggest that the presence of neonatal risk factors distinguishes APPIS from PVI. Collectively, these results suggest that NAIS and APPIS may often represent the same disease, differing only in the timing of clinical presentation. On the contrary, common cortical involvement in APPIS creates additional late clinical presentations and long-term outcomes including seizures and nonmotor developmental delays.5,64 Attributable in part to a strong selection bias (ie, only late symptomatic children will present and be diagnosed), APPIS outcomes seem relatively severe compared with other perinatal stroke disease states. Hemiparetic cerebral palsy is the most described morbidity, present in >70% to 80%.5,20,21,61 Not surprisingly, cortical involvement seems to predict nonmotor outcomes including language and cognitive morbidities as well as epilepsy.5,23,63

However, detailed studies of all outcome elements discussed above are still awaited in the APPIS population.

Periventricular Venous Infarction (PVI)

PVI refers to term born children with preterm, in utero germinal matrix hemorrhage with secondary medullary venous infarction. These commonly damage the corticospinal tracts, resulting in hemiparetic cerebral palsy presenting as PPIS. Well described in delivered preterm infants, current evidence suggests in utero occurrence is also common65 and can be confirmed by modern magnetic resonance imaging in young children.56,67 With accurate classification only occurring recently, PVI outcome studies are few. Although the same mechanism commonly occurs in delivered preterm infants, extrapolation of outcome studies from this population are limited by the many confounders of preterm birth. Most PVI cases present with an isolated hemiparetic cerebral palsy.64 Compared with arterial perinatal stroke that typically affects the middle cerebral artery territory with relative sparing of the leg, the lower extremity is more often affected in PVI.5 Sensory deficits may be less common in PVI with some evidence that sensory tracts can reroute around these early, small lesions.68 Consistent with their isolated, subcortical location, PVI seem to have a much lower risk of cognitive and behavioral disorders.5 Recently, we demonstrated that cortical gray matter volumes are also diminished in PVI,69 although the clinical significance is uncertain. Particularly for differences of timing and location, PVI provides an important comparative outcomes model among the perinatal stroke syndromes.

Summary

Life after perinatal stroke can certainly be good. The high level of functioning attained by many children despite large brain lesions is a remarkable testament to the potential power of developmental plasticity. However, it is clear that such early injury places many other children on an abnormal developmental trajectory with functional consequences.

How the interplay of multiple disordered functions in individual children may combine to impact the eventual outcome is of great interest. A child with great developmental potential may be stymied by pathological electrographic brain activity during sleep. Another child highly capable of acquiring new motor skills may fail to gain practical function because proprioceptive deficits prevent him or her from knowing where his or her hand is in space. Another with normal intelligence but an attention disorder may not be able to engage in school, therapy, or sports that could each improve function. With improving recognition and measurement, an integrated understanding of how these multiple factors dictate outcomes in individual children will be a major challenge of perinatal stroke research going forward.

Disclosures

Dr Kirton has provided expert medicolegal opinions related to perinatal stroke.

References


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Adam Kirton and Gabrielle deVeber

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