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Cerebrovascular Disease in Children: Recent Advances in Diagnosis and Management

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Abstract

Cerebrovascular disease in children manifests in many forms, all of which have devastating and long-lasting effects. Recent advances in diagnostic imaging have revealed that this condition is much more common in the pediatric population than previously believed, affecting as many as 1 in 1500 neonates and 1 in 3000 children. The underlying mechanisms that cause stroke—ischemic stroke, sinovenous thrombosis, and hemorrhagic stroke—are only beginning to be understood; however, progress has been made toward better understanding the mechanisms of disease, particularly in the fields of genetics, inflammation, and thrombus formation. Furthermore, new imaging techniques, and better understanding of how to use imaging in managing stroke, have enabled practitioners to more quickly and accurately identify cerebrovascular disease type in children, which is key to mitigation of negative outcomes. The 2010 Neurobiology of Disease in Children symposium, held in conjunction with the 39th annual meeting of the Child Neurology Society, aimed to (1) describe clinical issues surrounding childhood stroke, including diagnosis and acute care; (2) discuss recent advances in the understanding of the pathogenesis of childhood stroke; (3) review current management of and therapies for childhood stroke, including controversial therapies; and (4) establish research directions for investigators. This article summarizes the speakers' presentations and includes an edited transcript of question-and-answer sessions.

Keywords

cerebrovascular disease; stroke; arterial ischemic stroke; cerebral sinovenous thrombosis; hemorrhagic stroke; thrombosis; neurovascular; neuroimaging

CLINICAL ISSUES

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Insights From an Emerging Field

Gabrielle deVeber, MD, The Hospital for Sick Children, Toronto, Ontario, Canada

Dr deVeber discussed recent insights in diagnosis and initial treatment of pediatric stroke and how the condition differs from adult stroke. Pediatric stroke is considered an emerging field. The incidence of pediatric stroke is 1 in 5000, and if hemiplegic cerebral palsy due to vaso-occlusive stroke is included, the number could be as high as 1 in 3000. Additionally, cerebrovascular disease is 1 of the top 10 causes of death in infants younger than 1 year. Finally, 20% to 30% of children with arterial ischemic stroke will have recurrent strokes, even with treatment. Stroke in children differs from stroke in adults. Not only is it rare, but its presentation is subtle—particularly in infants—and even with a focal hemiplegia there is a wide differential diagnosis. Coagulation mechanisms, the arteries, and the neurological systems are all different in children, and each of these plays a large role in stroke. The causes of pediatric stroke do not include atherosclerosis, so a myriad of other risk factors and associations exist and are unique for each age group. The causes of pediatric stroke are poorly understood, and although this is a fertile area of research, clinical trials in the field are lacking. Currently, any treatment guidelines or tools being used to treat children with stroke either come from the field of adult stroke or are based on empirical information.

More than 95% of children with ischemic stroke have an underlying thrombus occluding an artery or a vein, and our understanding of clot pathogenesis in children is increasing. Whereas in adults, platelet clots predominantly form secondary to atherosclerosis, in children and infants there is likely a higher fibrin composition, which may require a different treatment strategy. Although anticoagulation is typically used, it is not known whether anticoagulation is more effective than aspirin. There are also major clinical challenges, the most significant of which is that the diagnosis is not made and the stroke is missed entirely or that the diagnosis is severely delayed and by the time the diagnosis is made, the infarct is much larger.

The clinical presentation or diagnosis of stroke in children can be delayed because focal neurological signs, the classic hemiplegia expected in adults, do not occur as frequently in infants or in children with stroke. In newborns, focal neurological signs appear in fewer than 25% of patients. Children with stroke have hemiparesis about 80% of the time, but an examination of seizure incidence shows that newborns with stroke have a much higher prevalence of seizures. This underscores the clinical challenge of identifying children at the onset of infarction.

On average, children with new neurological symptoms arrive at the hospital 1.7 hours after onset of symptoms, compared with approximately 8 hours in adults. Regardless, brain imaging is often delayed because stroke is not considered as quickly in the differential diagnosis in children as it is in adults. The average delay to neuroimaging in adults is 2 hours, whereas in children it is nearly 8 hours.

When considering treatment in advance of clinical trial data, the first thing to consider is improving outcome while avoiding complications. Only one-third of newborns and 24% of older children are neurologically normal after a stroke. Furthermore, these statistics do not

account for cognitive or silent deficits in learning. Good treatment also attempts to prevent death from swelling and herniation due to the stroke and epilepsy, which is seen in 17% of newborns and 11% of children. These efforts are in addition to prevention of recurrence or, in the case of newborns, concurrent systemic thrombus. Of major importance is the recent observation that the neurological examination of newborns with stroke does not reveal the full extent of brain injury. Neurologists and neonatologists need to be aware that newborns grow into their deficits; as a patient's brain matures and myelinates and as developmental milestones are reached, the deficits emerge.

The current arsenal of treatment options is limited. First, there are antithrombotic treatments to prevent clot formation, including aspirin as antiplatelet therapy and anticoagulant medications to prevent the fibrin clot formation. Additionally, a safety and dose-finding study for tissue plasminogen activator has just been approved. However, the guidelines have been developed to delineate the components of the very important basic care of acute stroke, including guarding a child with an evolving stroke against seizure, low blood pressure, and low blood glucose, all of which are likely to substantially increase the size of the infarct. Again, the utility of these guidelines depends on swift and accurate diagnosis.

Disease-specific treatments are available for other forms of cerebrovascular disease. For instance, indirect revascularization can be used for the treatment of Moyamoya, chronic transfusion therapy for sickle cell disease, and immunosuppression for vasculitis. However, even with these trial-supported disease-specific interventions, many children are left with a neurological deficit. Therefore, rehabilitation after stroke in childhood is a rich area for research.

The advancement of pediatric stroke research requires extensive collaboration across laboratories, disciplines, and geographic boundaries. The International Pediatric Stroke Study is an example of this approach. An early study from a Canadian national collaboration yielded several conclusions. First, arterial ischemic stroke (75% of incidents) and sinovenous thrombosis (25% of incidents) were seen at a combined rate of at least 2.2 per 100 000 children per year. Second, 25% of children with stroke are newborns at the time of the event. Third, males were more commonly affected in all stroke subtypes. The International Pediatric Stroke Study was created in January 2003 and is an observational study—no interventions planned—intended to provide a vehicle for randomized, controlled trials. This study now includes 250 investigators, 150 centers, and 2500 enrolled patients. Additional separate collaborative studies are investigating other risk factors for stroke, such as infections, as well as the previously mentioned tissue plasminogen activator study.

In conclusion, childhood stroke is different from adult stroke. There are multiple mechanisms, some age-related, and these must be understood to advance research in the field as well as treatment of the individual child. Adverse outcomes affect the majority of children who experience stroke, and the effects can be life-long. Collaboration with researchers in adult stroke is also needed, because much of what has been learned about adult stroke can be extrapolated to pediatric stroke. Finally, increased lobbying of government agencies and the American Heart Association to rapidly bring more resources to children with stroke is needed as the field quickly expands.

Perinatal Arterial Ischemic Stroke

Adam Kirton, MD, MSc, FRCPC, Alberta Children's Hospital, Calgary, Alberta, Canada

Dr Kirton focused on neonatal arterial ischemic stroke, reviewing the current understanding as well as highlighting future directions. He also discussed other types of perinatal ischemic stroke, which the National Institutes of Health defines as "a group of heterogeneous disorders in which there is a focal disruption of cerebral blood flow secondary to arterial or venous thrombosis or embolization."[1] However, rather than being just one disease, arterial ischemic stroke is a collection of specific diseases resulting in focal disruption of blood flow to an area of the brain or blockage of an artery or a vein resulting in focal injury. Furthermore, neuroimaging has revolutionized the diagnoses made and awareness of these individual diseases.

Perinatal stroke is far more common than previously thought, and although advances have been made, it is still not diagnosed or understood properly. In a large proportion of patients there is no understanding of what precipitates a stroke, and because of this there is little in the way of prevention or treatment strategies. For an adult, even with numerous risk factors, the highest risk of having a stroke in any given week is 1 in 3000. However, the incidence of perinatal and neonatal arterial ischemic stroke can be as high as 1 in 1500 in the first week of life, a very significant risk.

Focal occlusion of an artery in the brain, which presents acutely in the newborn, can be fairly easy to recognize: a well-looking term baby has a focal seizure, imaging is conducted, and the stroke is recognized. However, cases are not always this straightforward and can often be quite difficult to diagnose. A high index of suspicion is necessary, because some infants will present as if they have a common variety of neonatal encephalopathy. Patients may look asphyxiated, have diffuse neurological findings, and have signs of acute intercurrent illness. Additionally, it is rare for infants to manifest focal deficits. In these cases in particular, diagnosis rests on imaging. Although computed tomography (CT) and ultrasound can be of service, magnetic resonance imaging (MRI) is the imaging modality of choice. A diffusion scan with an apparent diffusion coefficient map clearly shows restricted diffusion in known arterial territory, making an arterial ischemic stroke very easy to diagnose much of the time.

Although MRI is improving our understanding of these diseases, magnetic resonance angiography can also help visualize blood vessels in the brain. An ever-increasing number of sequences can be used to inform a treating physician of the nature of a particular injury, including identification of hemorrhagic transformation and other elements. Incorporation of this type of neuroimaging into an institutional neonatal neuroimaging protocol is important because often the diagnosis is not recognized until the infant is in the scanner. It is important to gather all of the information needed to make a diagnosis, and this technology has great potential to help advance understanding of these types of cerebrovascular diseases. The classic lesion that appears in these infarcts is a large-artery occlusion, usually the middle cerebral artery, involving the cortex as well as subcortical structures. For reasons not fully understood, the left side is more often involved than the right. Less often the posterior circulation is involved. Lesions are often multifocal, suggesting a proximal source of

embolization, and although hemorrhagic transformation of infarcts is often seen, its clinical significance is not known.

When considering risk for stroke, many perinatal factors must be considered. For instance, case-control data indicate infertility as a factor, although it is not understood why. Prenatal conditions such as chorioamnionitis, preeclampsia, and gestational diabetes also increase a neonate's risk for stroke. Cesarean sections are more common in neonates with stroke, although the reasons necessitating those procedures are often not recorded. Neonates who need resuscitation or show signs of systemic illness exhibit higher rates of stroke, but it is not understood how these factors contribute to the formation of a clot and the blockage of an artery. A major suspected origin of perinatal stroke, but a very difficult cause to study, is the placenta. Congenital heart disease is also certainly a risk factor, although it probably accounts for 20% or fewer of cases and therefore cannot tell the entire story. The same can be said for prothrombotic conditions. In case-control studies, several prothrombotic factors have emerged as significant, but the mechanism of contribution to the stroke is still to be determined. In many cases, the cause simply isn't known.

How does a physician assess a child with arterial ischemic stroke? Many or most of these patients have seizures, so they undergo an electroencephalogram or are monitored. Although a cardiac evaluation is reasonable, in a child with no signs of cardiac disease the yield is very low. Prothrombotic testing is also reasonable, but interpreting the meaning of these results can be difficult, particularly in a center without the normative values in a newborn. Placental pathology should be sought, when available, and although most of these patients undergo infectious and metabolic studies in due course, they often do not tell much about the cause of stroke.

Not all perinatal stroke is an acute arterial event at birth. One way to consider perinatal stroke is based on when the child presents (eg, symptomatic newborns with arterial ischemic stroke), but a large number of children are late presenters in whom imaging shows old focal arterial lesions. Data from the Alberta Perinatal Stroke Project, a population-based cohort, show that the numbers of patients are comparable among all 3 perinatal stroke syndromes, which suggests that acute neonatal arterial ischemic stroke may be only a third of perinatal stroke cases. In fact, compiled data from all 3 syndromes show that the incidence approaches 1 in 1000 live births.

Although prevention of perinatal stroke is very far off, research areas that may be more fruitful in the short term are treatment and rehabilitation. Although the published consensus guidelines for neonatal arterial ischemic stroke do not always agree, they do indicate that anticoagulation is reasonable if there is a known cardiac source for the stroke. The most important point, however, is to protect the vulnerable brain of a newborn with a fresh stroke. Rehabilitation, as well, holds much promise for development. Given that the ability to prevent perinatal stroke is so far off, the burden of morbidity will persist, and it is significant. Outcomes are becoming more possible to predict as more is understood about these strokes. Because neonates grow into their deficits, time is the best predictor of outcome. However, with greater understanding of the utility of imaging, identifying where a lesion is located, what type of lesion exists, and the size of the lesion and identifying

diffusion changes also help to predict outcome. Earlier studies showed that examining diffusion changes outside of the infarct going down the cortical spinal tract can help predict motor outcome. This has been shown to be true not only in newborns but also in children and adults as well as in animal models of perinatal stroke; imaging is, therefore, an important tool for predicting more specific long-term outcomes.

Although traditional therapies help reduce the physical disabilities that most children have after a stroke, there is little evidence to support their effectiveness. However, new treatments such as constraint therapy and brain stimulation aim to improve function. Perinatal stroke may be the perfect model for studying constraint, but how does one learn what is changing in the brain when a child receives constraint therapy? Advanced technology such as transcranial magnetic stimulation, functional MRI, and diffusion tractography can help investigators understand how the developing brain responds after a focal lesion and perinatal stroke have manifested. Transcranial magnetic stimulation, in particular, can reveal areas of cortical excitation at the cellular level as well as interhemispheric relationship in the brain. Mapping these areas can give increase our understanding of how the brain responds after a stroke at a young age and how the 2 sides of the brain try to control the weak side of the body, which will help researchers develop new interventions.

Diagnosis and treatment of this very common condition are improving, and imaging is the key. Although the causes are not completely understood and outcomes are poor, perinatal stroke is an excellent model of developmental plasticity. In understanding this, researchers gain the ability to improve long-term outcomes.

Childhood Arterial Ischemic Stroke

Heather Fullerton, MD, MAS, University of California, San Francisco, San Francisco, California

Dr Fullerton briefly discussed stroke classification, how to recognize symptoms of a stroke in a child, first steps to take if a practitioner suspects a stroke, and basic intensive care unit management. Stroke in children can be broken down into ischemic stroke and hemorrhagic stroke. More will be mentioned later concerning hemorrhagic stroke, but whereas hemorrhagic stroke accounts for a small proportion of adult stroke, it accounts for 50% of pediatric stroke. Thus a discussion of ischemic stroke in children covers only about half of the strokes that occur in children. Stroke is seen at all different ages in children but occurs more frequently at less than 1 year of age and also in the teenage years. Additionally, stroke occurs more in males than in females. Even excluding cases related to trauma does not fully explain the gender difference, so there must be a factor involved that goes beyond trauma. African American children also have a higher incidence than white children, even when accounting for sickle cell disease.

The most common presenting feature of pediatric stroke is hemiparesis. In different series, hemiparesis has been observed in frequencies ranging from 50% to 100% (in one small series), but the onset of the deficit is not always as characteristically abrupt as in adult stroke. An adult presenting with this stroke has a very abrupt-onset deficit that helps practitioners to differentiate it from other events, such as a complicated migraine. In

children, the presentation is not so abrupt. In many cases it will progress over a matter of hours and can wax and wane. Likely this is related not simply to parental perceptions but rather to differences in cerebral perfusion in children that may allow them to maintain perfusion when they have an occluded vessel, causing their symptoms to wax and wane over a period of time. The other major challenge is that children often experience a seizure followed by weakness (Todd's paresis) and it may be difficult to promptly recognize a stroke. Some children who present with what appears to be Todd's paresis have actually had a stroke. Many of these patients will have headache at their stroke ictus, and it will appear to be a complicated migraine.

The most common location for childhood stroke is the middle cerebral artery, but stroke occurs in other locations. However, small lacunar strokes are rare in children. Cerebellar strokes are particularly dangerous, because symptoms are often mild but the stroke can be fatal. A total central ataxia can be relatively mild, but brainstem compression from the edema can be life-threatening.

With a suspected stroke, what should be the first steps? In the clinic this is a neurological emergency, and these patients need to be brought to the emergency department. Once a patient arrives, practitioners should work through the ABCs, put the child on oxygen, order basic laboratory tests, and then do emergent head imaging. If an MRI cannot be obtained immediately, then CT scans are worthwhile because—as previously mentioned—half of all strokes in children are hemorrhagic, and CT is sensitive for hemorrhage. However, CT is insensitive for acute ischemic stroke. Evidence of an infarct will not be visualized for at least 6 to 12 hours, and MRI with diffusion-weighted imaging is needed to identify arterial ischemic stroke. However, diffusion-weighted imaging becomes positive very quickly, so a diagnosis can be made within minutes. The importance of imaging the neck cannot be overemphasized. Intracranial vascular imaging is considered standard, but images of the neck can also be informative. If an MRI is inconclusive, practitioners should consider performing a traditional angiogram. Once stroke is confirmed, the child needs to be admitted to the intensive care unit for management and frequent neurological monitoring.

Once arterial ischemic stroke is diagnosed, a number of goals for the early treatment phase must be met. First and foremost is reperfusion, reducing the size of the stroke by reopening that vessel. A number of hyperacute strategies are being used in adults, but these are unstudied and controversial in children. An intravenous tissue plasminogen activator dosing and safety trial has now been approved and will begin in 2011, but certain conditions are associated with very high mortality. Therefore, in certain cases, such as basilar artery thrombosis, it may be appropriate to consider hyperacute therapies. This policy must be discussed at each center and a decision made in advance of the first child presenting.

The second goal is to protect the ischemic penumbra and to perfuse pial collaterals. Fortunately, children have excellent pial collaterals. If one considers the cerebral circulation as a large tree with branches, there are connections at the end of the branches and so blood vessels will connect through the meninges, through these pial collaterals. If a middle cerebral artery is occluded, it is possible that the anterior cerebral artery and the posterior cerebral artery can provide collateral flow to the middle cerebral artery territory. This is why

a fair number of children who have a proximal middle cerebral artery occlusion end up with a deep infarct with sparing of the overlying cortex—because they have very good pial collaterals. It is important in the intensive care setting to take advantage of those excellent pial collaterals and to lower the head of the bed to increase perfusion to the brain. Whereas most adults with stroke are hypertensive at baseline, children generally are not, so it is important to ensure that they at least stay normotensive. These patients also need to receive extra fluids, at least 1.5 to 2 times maintenance fluids with normal saline, not half normal saline, and pressors if necessary, particularly if the child is receiving sedative medication. There is not a great deal of direct evidence for these supportive measures, but it is important to avoid complications such as hyperthermia and hypoglycemia or hyperglycemia. There is strong evidence in the animal literature to support this, and there is also some adult literature from which pediatric researchers are currently extrapolating.

Third, and possibly most important, is observing for neurological decompensation. It is important for families to realize that a child will get worse before he or she gets better. Maximum swelling from a stroke occurs 3 to 4 days after the stroke. In cases of middle cerebral artery stroke, this is what is referred to as malignant middle cerebral artery syndrome. After middle cerebral artery infarct, the brain swells and edema compresses the anterior cerebral arteries, which can compound the original stroke with additional ischemia. Herniation is common when middle and anterior cerebral artery infarcts coexist, and so hemicraniectomy may be necessary as a life-saving procedure.

Subsequent to treating a first stroke is preventing a second, and a large part of preventing a recurrent stroke involves identifying the cause of the first. Data from a population-based study in northern California indicated that neonates have a low risk of recurrence, but older children are at much higher risk of recurrence; approximately 20% of the children in this study eventually had a recurrent stroke.

Among a long list of potential causes of childhood stroke, there are several to highlight. Of the patients in the northern California study who received vascular imaging, vasculopathy seemed to account for a quarter of the strokes. A prospective study in the United Kingdom showed that 80% of previously healthy children with a stroke had a large-vessel arteriopathy. Additionally, the population-based study showed that children with abnormal vascular imaging because of a vasculopathy were at highest risk for having a recurrent stroke; approximately two-thirds of these patients had a recurrent stroke. The vasculopathies identified were a heterogeneous group of disorders: arterial dissection, with tearing in the wall of a blood vessel; vasculitis, with beading of multiple blood vessels; fibromuscular dysplasia; and other large-vessel vasculopathies that simply are not yet understood.

A number of the vasculopathies observed were idiopathic, with focal stenosis. This tends to involve the distal carotid or proximal middle cerebral artery or anterior cerebral artery and can be referred to by different terms—neurologists often use the terms *transient cerebral arteriopathy* or *focal cerebral arteriopathy of childhood*, whereas rheumatologists use *primary central nervous system vasculitis*, despite debate about whether the condition is truly a vasculitis. The Vasculopathy and Infection in Pediatric Stroke study is currently focusing on this and trying to further understanding. Additionally, Moyamoya disease, along

with the congenital disorder face syndrome and genetic syndromes such as Williams syndrome, increases risk for stroke.

In summary, childhood stroke is a heterogeneous disorder. Early recognition is important, considering hyperacute therapies, especially as a tissue plasminogen activator study begins to move forward. Institutions should consider how this condition can be recognized early; how practitioners can be prepared to offer hyperacute therapies, especially in high-morbidity strokes like basilar artery thrombosis; and how to be vigilant in preventing secondary complications and recurrences, particularly in children in whom there is so much opportunity to prevent secondary brain injury.

Perinatal Cerebral Sinovenous Thrombosis

Linda DeVries, MD, Wilhelmina Children's Hospital, Utrecht, Netherlands

Dr DeVries delivered an address that introduced perinatal sinovenous thrombosis, focusing on diagnosis and the importance of imaging, early treatment, and outcomes. Cerebral sinovenous thrombosis occurs following the occlusion of one of the major cerebral veins and has an incidence in neonates between 1 and 12 per 100 000. As in arterial ischemic stroke, males are known to be more at risk, and presentation is often very nonspecific. Mortality in cerebral sinovenous thrombosis can be high—up to 19% in the literature—and the condition results in adverse outcomes in approximately half of children. Cerebral sinovenous thrombosis is now being recognized more frequently in the newborn period because of the increased use of MRI when infants present with neonatal seizures. Data from the International Pediatric Stroke Study show that 36% of pediatric cerebral sinovenous thrombosis occurs in the newborn period. The clinical presentation of these children commonly includes seizures or apneas (in 76% percent of patients), but on standard or continuous 2-channel electroencephalogram these apneas also appear to be due to seizure activity. There are a variety of other symptoms, and many of these children will have more than one of the clinical symptoms at the time of presentation. These findings were validated by a recent study performed in the Netherlands taking children from 5 different centers. Generalized seizures were most common. Some patients had partial seizures or hemiconvulsions, and quite a large number of children presented with apneas (17%), bringing these 3 groups also up to 73% of patients. However, a child can also be completely asymptomatic

When trying to diagnose cerebral sinovenous thrombosis when children arrive in an institution, the first step is to perform cranial ultrasound; using Doppler and especially power Doppler can be very helpful. MRI should also be performed as soon as possible and then magnetic resonance venography as part of a neonatal protocol. A scheme published in 2001 by Gabrielle deVeber[2] shows that the superior sagittal sinus is most commonly affected in this age group, followed by the lateral sinuses and the straight sinus. In another study showing that the sinuses are most commonly affected, again the superior sagittal sinus was most common—involved in two-thirds of cases—followed by the transverse sinus and the straight sinus. However, often children were included in more than one category. Several years ago a very important observation was made: in children who are born at term and who present with symptoms that indicate an intracerebral hemorrhage, often with an associated

unilateral thalamic hemorrhage, cerebral sinovenous thrombosis should be considered. After magnetic resonance venogram or MRI, cerebral sinovenous thrombosis was found significantly more often if the child had associated unilateral thalamic hemorrhage. Additionally, hemorrhagic infarction is more often associated with a worse outcome, and the side of the lesion correlates well with the sinuses involved. However, there is not a great deal of detailed information in the literature about associated lesions, and information about preterm babies is scarce.

Dr DeVries and colleagues described different patterns of associated brain lesions in preterm and term infants with cerebral sinovenous thrombosis and assessed whether these patterns are related to gestational age at onset. Neonates born between 2002 and 2009 were enrolled, and clinical data and follow-up data were collected until at least 2 years of age. The protocol was to perform MRI/magnetic resonance venography at the time of diagnosis and again at 3 months. All available magnetic resonance scans were reassessed, confirming the diagnosis of cerebral sinovenous thrombosis, and patterns of associated lesions and their severity were recorded and compared between the different gestational age groups.

The first observation was that there was a difference in involvement of the different sinuses. In this population the straight sinus was most commonly affected (87% of patients), followed by the superior sagittal sinus and the lateral sinuses. Altogether, there were 28 newborn infants with available MRI, and cerebral sinovenous thrombosis was confirmed in 24 of these infants. Six of these patients were born prior to 36 weeks' gestation, and 18 were born beyond 36 weeks. In all but 2 of these infants, associated brain lesions were observed, and there were large differences between preterm and term neonates. It was also very common to find that several sinuses were affected, and in some patients all the sinuses were involved. Concerning associated lesions in the brain, in the preterm population 5 of 6 had severe associated white matter lesions. In the term infants, however, an intracerebral hemorrhage was more common and usually associated with a unilateral thalamic hemorrhage and/or punctate white matter lesions.

Most studies published to date show that almost 50% of children with cerebral sinovenous thrombosis have at least one moderate or severe impairment, and not surprisingly there is an association between infarction and impairment at follow-up. The question of whether to treat these patients is complex, at best. A 2010 paper from *Pediatrics* suggested that if there is an intracranial hemorrhage, it is best to delay treatment, repeat the magnetic resonance venogram in 5 to 7 days, reconsider if there is propagation of the clot, and then treat these children mostly with low-molecular-weight heparin and repeat the MRI after 6 weeks or 3 months after the therapy has been given to see whether there is recanalization of the thrombus. Another paper in the *Journal of Pediatrics* looked at 84 infants with isolated cerebral sinovenous thrombosis across 10 different countries, 50% of whom were treated; nontreatment was predicted by being born in the United States or by involvement of the deep venous system. In 15 patients seen by Dr DeVries and colleagues,[3,4] 10 of these children were treated with low-molecular-weight heparin without any apparent complications.

In conclusion, cerebral sinovenous thrombosis very often remains undiagnosed and should be considered in any infant presenting with seizures, especially in the context of

dehydration, meningitis, or intracerebral hemorrhage on ultrasound, and especially with a thalamic hemorrhage. MRI or magnetic resonance venography should be performed whenever possible, and therapy should be considered.

Childhood Cerebral Sinovenous Thrombosis

Fenella Kirkham, MBBS, UCL Institute of Child Health, Southampton, England

Dr Kirkham continued the discussion on cerebral sinovenous thrombosis commenced by Dr DeVries but set out to couch the information in the context of childhood cerebral sinovenous thrombosis rather than perinatal cerebral sinovenous thrombosis. Like perinatal cerebral sinovenous thrombosis, childhood cerebral sinovenous thrombosis is a diagnosis that is often missed; in fact, according to data presented, the diagnosis rates in neonates—despite being lower than actual incidence rates— exceed those of children. As an example, Dr Kirkham presented data from her tenure at the Hospital for Sick Children in London,[5] published in *Annals* in 2003, focusing on arterial stroke, as well as some material on stroke mimics and other causes of vascular problems. From the data, it appears that only 5 children in 22 years presented with arterial stroke at the Hospital for Sick Children. Upon review of specific cases, however, it became clear that arterial stroke had been missed. For example, a 20-month-old female with otitis media (which is now recognized as a common trigger) and acute neurological deterioration who is semiconscious on presentation and has thalamic involvement should point to the possibility that this is a venous problem. This child had demonstrated transverse sinus thrombosis on parenchymal imaging. If one were looking for cerebral sinovenous thrombosis, a venogram would not even be needed in this case, but the cerebral sinovenous thrombosis was missed until later further examination.

Another child, who was a transfer from an outside hospital, presented only with very mild hemiparesis. In fact, the child simply changed hands; that is, it looked as though he was going to be right-handed, and then he became left-handed. The child then presented with a more obvious hemiparesis and had an obvious cortical infarct. In the end, a formal arteriogram was needed to prove the venous sinus thrombosis. As an additional complicating factor, he had chronic, difficult to manage iron deficiency, which was not given much weight at the time. However, after this child was compared with other children with acute neurological problems, it became clear that the iron deficiency was much more significant. A patient from Southampton with a chronic hemolytic anemia presented with severe neurological symptoms, and a venogram showed a chronic sagittal venous sinus thrombosis. Anticoagulants resolved the neurological symptoms almost immediately. The patient was ultimately diagnosed with lupus, a condition in which it is easy to miss both arterial and venous stroke. Another patient, a child with hemoglobin sickle cell disease, who was actually included in a longitudinal study, presented with severe headaches. Although he was attended to by neurosurgeons several times because of a shunt he had in infancy, for what is now suspected must have been ventricular dilatation secondary to a venous thrombosis, the diagnosis was not made at the time of treatment. Again, upon review, a straight sinus thrombosis was visualized on the CT scan by a radiologist.

Having realized that cases were being missed, investigators conducted a retrospective examination of cohort data of 36 children presenting to pediatricians, that is, excluding

neonates and those with acute presentations, and 6 children with subacute presentations, for a group of 42 children aged 3 weeks to 13 years, with a slight predominance of boys (n = 27), which is in agreement with other published stroke data. Children with cerebral sinovenous thrombosis are less likely than children with arterial stroke to have a hemiparesis but are more likely to have a parietal infarction. There was a trend for an excessive occipital and thalamic infarction, which means that if a child presents with what appears to be an infarct on parenchymal imaging, which is not in the vasoganglia and not obviously a middle cerebral artery infarct, particularly if arterial imaging is negative, cerebral sinovenous thrombosis should be strongly considered. The diagnosis is extremely difficult to make later, as the venous sinuses commonly recanalize, so the venogram must be done at the time of presentation. The study showed that children with caudate infarcts were more likely to have arterial stroke than venous, but otherwise it is important to consider the venous sinuses. When blood counts were performed, iron deficiencies were observed more commonly in children with venous thrombosis. A further consideration is a patient with a separate diagnosis who then has a stroke. It could be post varicella angiopathy or a dissection, but in actuality children who are already ill with cardiac disease, sickle cell disease, thalassemia, or lupus are more predisposed to sinovenous thrombosis because they have the risk factors already. These patients are often systemically not well, are often dehydrated, are more prone to infections, and may be anemic. Eighteen percent of children with venous sinus thrombosis had infections, and otitis media was a common cause as well.

There are more data about investigation than about diagnosis. Knowing the patient's history is important (acute systemic illness, chronic disease) but there is an opportunity to look for prothrombotic risk factors, both by taking a good family history and by investigating. There is continued debate on precisely which prothrombotic risk factors should be investigated, but several seem to be clear. The first is the blood count, which will have been done upon admission, but not all practitioners consider it. A ferritin analysis can also be instructive. Many factor V Leiden or prothrombin 20210 mutations have not been found in the European data, but the Canadian data and the German data have more examples of those disorders. In addition to the data on iron deficiencies, the data revealed a number of children with high factor VIII, which warrants further investigation. It is also important to exclude thyroid disease, because it can present with venous thrombosis. Either an antinuclear antibody or DNA binding study is appropriate, particularly if there is any suggestion that the child might have lupus. Also potentially useful is a homocysteine, depending on vitamin status, because treating with vitamin supplementations may help reduce homocysteine levels. Of course, if feasible, a full prothrombotic screen is most useful.

Recurrence of venous sinus thrombosis is less common than that of arterial stroke, although it does happen. In data pooled from French, Belgian, and Israeli studies[6] published in *Lancet Neurology* in 2007, 384 stroke survivors were followed for a median of 36 months. Of this patient population, just under 6% had a recurrent thrombosis, some systemic and some cerebral. There are some data to aid in predicting recurrence. Younger patients are less likely to recur, as are patients in whom the venous sinuses recanalize. In addition, patients who did not have recanalization of their venous sinuses were also generally iron-deficient, so further venograms may be worthwhile. In patients with relapsed risk factors, such as nephritic syndrome or inflammatory bowel disease, anticoagulation may be warranted to prevent

recurrence. IIGA20210 mutation— prothrombin 20210 mutation—also seems to be a risk factor for recurrence and is worth investigating, even when resources are limited.

To make these diagnoses, the most important tool is a high index of suspicion. Basic CT and MRI results should be examined with cerebral sinovenous thrombosis in mind. Computed tomographic venography is also justified in this circumstance. Further studies may require a practitioner to persist with magnetic resonance venography and even conventional arteriography. In management, the most basic measures are necessary: supportive treatment of the seizures, treatment of the iron deficiency, and anticoagulation if appropriate. An early trial showed a reduction in mortality for cerebral sinovenous thrombosis treated with anticoagulation—even in the presence of hemorrhage; subcutaneous heparin can be used while monitoring the anti-10A levels, but intravenous heparin can also be used with a switch to warfarin later on. Thrombolysis, thrombectomy, and surgical decompression may need to be considered, but these treatments are also controversial. Collaboration with intensive care colleagues is imperative to look for and treat seizures; monitor Glasgow Coma Scale score; monitor for focal signs, visual acuity, and fields; and, for those who are not anticoagulated, consider reimaging at 5 days to see whether there has been propagation. Continuous encephalographic monitoring may also be worth considering to detect seizures. Follow-up is often difficult, as these patients often are under the care of general pediatricians or intensivists, but is well worth the time in order to monitor and, if possible, mitigate outcomes.

Hemorrhagic Stroke in Children

Warren Lo, MD, Nationwide Children’s Hospital, Columbus, Ohio

Dr Lo gave an overview of hemorrhagic stroke in children but confined his talk specifically to intracranial hemorrhage and subarachnoid hemorrhage, deliberately omitting neonatal intraventricular hemorrhage and hemorrhagic conversion. Although hemorrhagic stroke is less studied than other forms of stroke and there are a number of uncertainties about treatment, the literature indicates that outcomes in children may be better than those reported in adults. Identifying the frequency of hemorrhagic stroke is difficult, and published case series tend to come from tertiary care centers. However, in a California statewide discharge database, 49% of children with *International Statistical Classification of Diseases and Related Health Problems* (*ICD*)-9 codes indicating stroke had codes for either intracranial or subarachnoid hemorrhage. In a United States national database from 2003, 45% of children with *ICD-9* codes for stroke in the primary position also had codes for hemorrhagic stroke. More recent, unpublished data show a 42% frequency of hemorrhagic stroke. The concern when searching administrative databases is that it can be difficult to identify and verify the diagnoses, but in the northern California study that Dr Fullerton previously mentioned, the codes were verified based on radiological presentation and clinical verification of the chart. In this verified population there was a higher incidence of hemorrhagic stroke than ischemic stroke. The proportion of hemorrhagic stroke is also higher in children than it is in adults. As seen in the adult literature, intracerebral hemorrhage ranges from 7% to 20% and subarachnoid hemorrhage ranges from 1% to 7%: in total, 15% to 20% of adult stroke, versus 42% or more of childhood stroke, 2 to 3 times the incidence of adult stroke. A search

of nontraumatic and exclusively surgical case reports for contributing factors in the past 25 years shows that approximately 48% of strokes stem from intracranial vascular anomalies, predominantly arterial venous malformations, aneurysms, and cavernous malformations. Approximately 10% come from brain tumors, approximately one-fourth come from other assorted medical causes, and in 20% of cases the cause is unknown. Interestingly, in studies that were reported before 2000 compared with studies that were reported after 2000, the proportions remained the same over time.

There are clearly differences in risk factors for pediatric stroke and adult stroke. In adult stroke, the risk factors are generally age, hypertension, smoking, and a variety of factors that are not present in the pediatric population, where the majority of stroke comes from intracranial vascular abnormalities. The same holds true for adult subarachnoid hemorrhage; the risk factors are generally age, gender, smoking, alcohol, and other risk factors that are not present in the pediatric population. Notably, aneurysms in children tend to occur in a much higher proportion in males than females. Males also tend to have a higher proportion of posterior circulation strokes and also of pediatric aneurysms, which often have much more complex structures than the typical aneurysms seen in the adult population.

Most patients who present at age 6 or older tend to have a constellation of features: headache, focal neurological signs, and altered level of consciousness. Seizures may or may not be a part of that presentation. The difficulty in detecting intracranial hemorrhage in younger children is that the findings tend to be nonspecific, and so children show up with irritability, seizures, altered level of consciousness, and nausea and vomiting, but they may not have focal findings and certainly are not able to report in terms of headache. CT scan is ideal in detecting intracranial hemorrhage in an initial exam, but in a patient who has a strong clinical suspicion of a subarachnoid hemorrhage, a lumbar puncture may be required to detect any evidence of sub-arachnoid hemorrhage.

The next level of evaluation is to identify possible causes for a source of hemorrhage. This would include looking for evidence of thrombocytopenia using a complete blood count and screening for clotting abnormalities by measuring prothrombin time, partial thromboplastin time, and fibrinogen. The next step is to detect intracranial vascular abnormalities, so imaging studies should include a magnetic resonance angiogram, a computed tomographic angiogram, or a catheter angiogram. The strength of a magnetic resonance angiogram is that it is noninvasive, but there are limitations for detecting an aneurysm that is smaller than 5 mm. A computed tomographic angiogram is sensitive to small structures, but the concern with radiation exposure of a computed tomographic angiogram is that the x-ray exposure dose is about 10 times that of a standard CT scan. The catheter angiogram is considered the gold standard but involves an invasive procedure and therefore may be less appealing.

Initially, all patients should be admitted for intensive care unit observation. In the case of infratentorial hemorrhage, early resection may need to be considered when clinical deterioration occurs. Seizures should be treated to prevent any increase in intracranial pressure. A routine resection of a supratentorial clot is not indicated, and the management of intraventricular hemorrhage is uncertain. For a subarachnoid hemorrhage, it is important to manage increased intracranial pressure, avoid hypotension and transient increases in

intracranial pressure, treat seizures when they occur, and, as has previously been mentioned, consider monitoring for nonconvulsive status epilepticus if there is an altered level of consciousness. Bleeding sources should be occluded early, if possible, particularly with an aneurysm, and interventional occlusion should be considered, if available. The patient should be observed for vasospasm, and if vasospasm is detected, treatment should be considered. No specific recommendations for this have been established, but treatment with calcium channel blockers may be appropriate.

There are clearly gaps in the medical knowledge of this subject, but the American Heart Association consensus for childhood stroke leaves no question about the management of increased intracranial pressure, and there is good evidence to indicate that severe coagulation defects should be treated. The guidelines are less clear for patients with aneurysms, treatment of subarachnoid hemorrhage, and routine evacuation of a supratentorial hemorrhage. Recommendations for management of pediatric stroke are based upon consensus guidelines, and there are limited or no clinical trial data to use as a guide for how often to monitor patients with aneurysms, whether there is a role for treatment of vasospasm, or whether there is a role for evacuation of supratentorial hemorrhages. However, when the pediatric experience is compared with that of adults, it could be said that adults labor with the same problems—a number of the guidelines for management of increased intracranial hemorrhage or subarachnoid hemorrhage in adults are also based upon consensus guidelines and lack randomized, clinical trial data to support those measures.

There are limited data that suggest that outcomes in children differ from outcomes in adults. In the adult data, a high mortality rate exists for intracerebral hemorrhage; at 30 days 40% to 50% of the patients have died, and of those survivors about half are dependent for activities of daily living. In the subarachnoid hemorrhage population at 30 days, one-third to one-half of the patients have died. The morbidity rate is 10% to 20%—lower, but still significant. In a retrospective case series of 56 children who had intracerebral hemorrhage, a series that included brain tumors, patients were followed for 11.5 years. Of this population, 20 of the 56 had died, 13 of the remaining population were paretic, and 16 of the population had no cognitive deficits. Another recently reported series of 30 patients from a consecutive cohort included brain tumors. The follow-up was approximately 9 months, and of this group 5 patients died and 4 had a poor outcome as defined by a Glasgow Outcome Scale. Predictors for outcome were ethnicity, the size of the intracranial hemorrhage, the presence of brain tumor, and the age of the patient. In a prospective cohort of isolated intraventricular hemorrhage that excluded brain tumors in 30 patients, follow-up was at approximately 3 months; of this population 1 died and 12 of the remaining had significant disability involving either neurological or cognitive function. Predictors of outcome in this study included intracerebral hemorrhage volume and altered mental state upon presentation.

Of 59 patients in an unpublished retrospective series at Nationwide Children’s Hospital, in a population that included patients with brain tumors and intraventricular hemorrhage, at 5 years 20 had died and 20 were lost to follow-up, leaving 19 patients who were assessed using a telephone interview paradigm. First, intracranial hemorrhage volume predicted death and poor outcome on a variety of measures, and second, diagnosis predicted outcome or predicted poorer outcome on a pediatric quality of life scale. In this study, intraventricular

hemorrhage and Glasgow Coma Scale score at presentation did not predict outcome. These outcome data suggest then that predictors for adult intracranial hemorrhage are not strong predictors for outcome in children, and this is partly because the risk factor profile is different between the age groups. Additionally, in the adult population a “do not resuscitate” status strongly predicts mortality, and there have been observations that aggressive management may be associated with lower mortality in adults. The question, then, is whether management of the pediatric patient population is different and whether outcomes in children are better than in adults. The current studies seem to give a mixed picture; this is likely attributable to the fact that whereas the longer term studies with broader inclusion criteria have higher mortality rates, all studies are relatively small and likely underpowered.

In terms of rehabilitation, stroke represents a model of acquired focal injury, and it suggests that intensive therapy such as constraint may be beneficial from a motor perspective, but what families are primarily concerned with are cognition, behavior, and social function, and currently there is no equivalent to constraint-induced modification therapy for those modalities. A number of laboratory research questions could be addressed, but models for intracerebral hemorrhage have a number of limitations and do not yet model pediatric hemorrhage accurately.

A number of clinical research questions are left on the table. What measures best predict cerebral hemorrhage outcome? How can we improve outcomes? Is there a role for neuroprotective measures, and ultimately, in terms of rehabilitation, can plasticity be modulated to improve outcome in this population? There are data that suggest this possibility. The argument can be made that hemorrhage is an important cause of pediatric stroke. The data are mixed, but suggested outcomes are better in children than the outcomes seen in adults, and although there are a number of uncertainties about treatment, this is a model for acquired injury that may lend itself to plasticity-related therapies.

Questions and Answers

Audience member: What is the opinion about prophylaxis for seizures in the children who have not had seizures yet, and does anybody treat for seizures before seizures occur?

Dr deVeber: It’s important to be very aggressive with seizure control. I believe the animal models, and I believe the adult data which indicate that seizures increase infarct size. Because of that we are monitoring neonates closely for subclinical seizures. We put them on continuous monitoring, but we also treat very aggressively. I don’t think we have any data to say whether you should or not, but if patients have even one seizure, we ride them through the next few days while the infarct is settling on anticonvulsants.

Dr Fullerton: I’ve seen a couple of kids with malignant middle cerebral artery syndrome who have probably been teetering close to the edge, did not receive prophylaxis, then seized, and then coned, herniated right at the time of seizure, probably because of the big autonomic surge tipping them over that edge, and so in kids with malignant middle cerebral artery syndrome who are having intracranial pressure issues, those are patients that I treat prophylactically with antiepileptic drugs.

Audience member: How is the decision made about types of imaging in pediatric stroke?

Dr Fullerton: We tend to use magnetic resonance angiography as a screening tool, and if an abnormality is detected, we order conventional angiography.

Dr Kirton: For the newborn, vascular imaging is not being done consistently enough. With new technology we can now obtain quality, noninvasive vascular imaging in the newborn, but it's not always easy. It takes some advocacy and some work.

Dr Lo: It also depends upon the level of clinical suspicion. We have had a couple of kids who have had multiple infarcts in the posterior distribution where there was a strong clinical suspicion that there was a dissection. Noninvasive magnetic resonance angiography and computed tomographic angiography did not demonstrate the dissection, but catheter angiography did.

Dr Kirkham: What you might do at the beginning depends on the site, but how far you push to get an MRI if you've just done the CT the following day or a catheter angiogram a couple of days later depends on how secure you are in having made the diagnosis and knowing you're on the right treatment track. We have to advocate now and do some studies to see which is the best protocol.

Dr DeVeber: The sensitivity for specific lesions around dissection is probably better for conventional angiography, but in addition to that, methemoglobin ring in the wall on plain MRI is very definitive. So we use conventional angiography whenever there is a magnetic resonance angiography abnormality that doesn't make sense and we're suspicious of something we need more detail on, and sometimes we use it when we've seen nothing on the magnetic resonance angiography. So we use it a lot. The other issue was the vascular imaging of venous disease, and that needs to be specifically thought about because you won't diagnose sinovenous thrombosis unless you specifically obtain vascular imaging.

Audience member: This is a question regarding neonatal stroke and fetal stroke: if we're going to diagnose fetal stroke that leads to neonatal stroke, do any of you have at least experience collectively or in your own centers about those proxies like Doppler abnormalities on prenatal testing or even epidemiological problems such as babies born from diabetic moms that would say, gee, this is a group of kids that we ought to get a fetal image on, and if there indeed is a stroke, down the road there may be treatments? It's kind of an open-ended question, but I thought I have you all together with your collective experience.

Dr Kirton: We are challenged still to identify the high-risk populations. We don't know what is predisposing babies especially to the fetal varieties of stroke, and we're a long way from identifying these at-risk moms in whom maybe we can do some kind of surveillance, some kind of early detection. Some of the pictures I showed and that are out there are often incidental findings or they're chronic lesions based on an abnormal ultrasound that something is going on in the brain. Fetal MRI now can give you beautiful pictures of infarcts that have occurred in utero although they usually have long since happened, and we still don't know why. So there is a lot of potential there, but the real challenge is identifying the

populations where you could put it to early use like you're suggesting, and we have to figure out what the at-risk populations are first before we'll be able to do that.

Dr DeVries: We don't see a lot of fetal stroke. They will not have any symptoms during the neonatal period so they will subsequently end up in the pediatric neurology department, but in the neonatal period, they are usually kind of silent if they would have been picked up antenatally even.

Audience member: Why is iron deficiency anemia a risk factor for lack of recanalization, and do we know if that could be a primary risk factor for thrombosis?

Dr Kirkham: We have a little evidence that it is a primary risk factor. We've looked, for example, in a couple of at-risk populations, unpublished as yet, but meningitis and also inflammatory bowel disease. So, these are large populations with those conditions who get venous thrombosis, and it looks to be the children with low hematocrit in particular. I don't know exactly why at all, but the things I wonder about are whether if you have small cells and particularly if you've perhaps got younger cells, which are stickier, you get more adhesion, then that may be a possible risk factor. But it's been something I've talked to the hematologist about for a long time, and I think it's something that would be very fruitful to look at on the laboratory side. It would be very exciting to collaborate with a young investigator to look at that.

Dr DeVeber: I agree that the deformability of the red cells may be one factor. The other intriguing factor is that the platelets are usually elevated, but not high enough for hematologists to worry about thrombocytosis and clot. But they're usually double normal in these children. The other thing is that our studies showed that it was a primary risk factor, so we took idiopathic children, looked for iron deficiency anemia, and then took normal children and looked for iron deficiency anemia, and we showed that it is a primary risk factor.

Audience member: I have some questions about the etiology of fetal stroke. Because it seems possibly to be related to the right to left shunting in the fetal circulation in the fact that you don't see recurrent stroke arterial stroke if you see it in the newborn period, does it pay to do any prothrombotic workup? It's expensive and not very revealing.

Dr Kirton: The placenta is the big unknown in fetal and perinatal stroke and a top suspect. There are a variety of diseases on the fetal side of the placenta that may be predisposing kids to this, some of which are primary thrombosis as a mechanism. In a sense it's one step removed, but that's the logic behind trying to understand where these clots are coming from, and if it's the placenta or if it's elsewhere, does having an underlying thrombophilia predispose you to that mechanism? And on a bigger scale there's lots of stuff out there that is yet to come down to large case-controlled studies looking at these individual types of perinatal stroke to tease out what the role of thrombophilia is, and I know we'll hear more later from Dr Massicotte, but there's still a lot that we don't understand.

Dr DeVries: One of the problems with neonatal stroke is that the babies often present after 12 to 24 hours with seizures, and by the time they come to us, the placenta has been thrown

away, so for the full-term population in contrast to our preterm stroke babies, we very often do not have access to the placenta, which is a real shame.

Audience member: Is there still any role for the use of hypothermia in the management of children with stroke? My second question: as our population of children has gotten larger—and it's not uncommon for me to see 6- and 8-year-olds who top 50 kg and are more prone to the diseases of obesity like diabetes and metabolic syndrome—are we also, as child neurologists, going to have to be more familiar with the management of the typical adult causes of stroke in our pediatric population?

Dr Fullerton: The first question will be answered this afternoon regarding hypothermia. With regard to the second question, that's still an open question. What is the role for some of these adult atherosclerotic risk factors? When we've looked at those in our Kaiser population, we did not find that obesity was a risk factor. In fact, our controls were obese because we realized that our modern controls compared to these old Centers for Disease Control (CDC) norms; our controls are obese, and our cases tended to have lower body mass indices than the controls for some reason, not even after controlling for chronic diseases like congenital heart disease. We did find that hypertension was a risk factor, although that seemed to be largely explained by underlying autoimmune diseases like lupus. And so it's not clear where that is on the causal pathway. Diabetes was also slightly more common, and smoking was more common in our cases than our controls, and this was basically just smoking documented in the charts by the primary care physicians prior to the stroke event, so it wasn't a history of smoking obtained after the stroke event because then we couldn't compare that to controls, but we had slightly more. It wasn't significant, but I think it's still an open-ended question.

Dr Kirton: It's an important thing to consider for the long-term follow-up. You heard all about the high recurrence risk and that if these kids have strokes when they're 5 years old, they're looking at decades of the same problems we're all supposed to pay attention to in regard to the health of our arteries. Is it more important for kids who have a scar on their artery and an arteriopathy that's healed but left a scar? Are they at heightened risk? Should we pay more attention to their exercise, diet, lipids, smoking, all the modifiable risk factors that adults are supposed to pay attention to? I don't think we know, but it makes good sense, and it's relatively easy to do. So, it's becoming more part of our practice to do that.

Dr Kirkham: One of the things I didn't look at when I was looking at the arterial strokes was the lipid profile, but we had some recurrences in children who did have high cholesterol, and it has been shown quite nicely that lipoprotein delay is a risk factor for recurrence, and so I'm certainly looking at lipid profiles as well as blood pressure to try and reduce the recurrence rate. I do think we need to look at this, although like Dr Fullerton we didn't find the obesity.

Audience member: Back to neuroimaging, given the proclivity to motion artifact, especially in young kids or kids who are frightened, what is the general protocol for MRI or magnetic resonance angiography? Are we using sedation, restraint? Is there any kind of consensus in that in the various clinical centers?

Dr Kirkham: We use general anesthetic for an MRI, and if you're set up for that, that's what you have to do. If you can't do that, then you can sometimes get a CT quickly enough to show where you are, and then you need an MRI the following day under general anesthetic.

Dr Fullerton: I agree with that; a big part of taking care of acute strokes at your institution is to talk to your anesthesiologist in advance, your radiologist, setting up a pediatric stroke protocol, and involving the anesthesiologist in that because you do have to get the buy-in of the anesthesiologist to do these in an emergent fashion.

Dr DeVeber: Just to follow on that, our anesthesiology department has, with some lobbying, accepted that acute stroke is a priority one in our institution, which is reserved for conditions that cause impending loss of life or limb within 4 hours. And we argued successfully that impending loss of hemisphere within 4 hours was probably just as important.

Audience member: I have 2 questions. The first—we talked about treating seizures aggressively. Would anybody hazard a guess as to what agent we should be using? The second question concerns the data that came out of Children's Hospital of Philadelphia with regard to kids who had cardiovascular procedures; the data showed that they had subclinical activity. Now, it's not the same thing, but should we be getting continuous monitoring, or are there some data to support a role for prophylaxis even before you've had seizures?

Dr Kirkham: I have some unpublished data to suggest that subclinical seizures are an important predictor of outcome in coma in general, and a lot of that is vascular, so if you've got access to electroencephalography (EEG) you should be considering some other data that have looked at that as well; in that data set, using a benzodiazepine reduced the frequency of seizures on EEG down the line, so I think usual practice is very reasonable. And Dilantin is a very good anticonvulsant, old-fashioned but very useful.

Audience member: Regarding the last question, we've just completed about a hundred children with complex congenital heart disease doing continuous EEG monitoring, and interestingly diazepines are used I believe in the intensive care unit as part of their postoperative workup and we've not been able to record any subclinical seizures in that group of patients, so probably diazepine is having a good effect in that population. I just wanted to make a small plea for neuroradiologists so as not to totally inundate the service. We've just done an evidence-based, hospital-wide look at the way we should screen for pediatric stroke coming through the emergency room together with our neurology colleagues and neurosurgeons, and the paradigm that we've come up with, which has some support now in the adult literature, is to get an unenhanced CT when the child hits the emergency room, particularly in light of the fact that we are looking toward intravenous tissue plasminogen activator as part of your study. But then we get a diffusion-weighted image, and this is a 1-minute study. It doesn't require sedation. As we've all heard, within 20 minutes you will have a positive scan, and I think it's a very good screening process. We've already started to deploy this, and in the first 12 patients, only 1 child came up with a positive diffusion-weighted imaging. It saves an enormous amount of time, and while we're not preventing that child from being worked up in the future, at least for the intravenous tissue plasminogen

activator study we're making a definitive diagnosis off the bat as to whether this child has a completed ischemic stroke.

Audience member: It has been a relatively common experience with me, particularly with children referred from rural settings: their first neurological consult is at 12, or 18, or 24 months for their mild cerebral palsy or the onset of their focal seizure, and you review their records and examine them and there's no question they had some sort of perinatal or intrauterine stroke. So, when you see them at that age, how far are you going with thrombophilia workups? What do you do to look at this? These are often young couples. They're going to look at future children. What do you do?

Dr Kirton: We see a large population of those kids. I sound like a broken record saying that we don't know. Particularly in the presumed perinatal stroke population, the one you're referring to, the late presenters, the data are scarce. There are a couple of small studies about identifying types of thrombophilia are you looking for? It's particularly important because we're dealing with more than one disease, a point I tried to make that some are arterial strokes like the acute neonates, but some are these venous infarcts in the white matter and probably very different mechanisms. We have some preliminary data that say thrombophilias look more common in both of those groups, but we don't know, and so we're doing very comprehensive workups in a case-controlled fashion to try and figure out what it all means. In the clinical setting, screening for thrombophilia is not unreasonable, but you need to be careful that your center knows how to interpret age norms and that you can interpret the results. There is almost no recurrence rate, so this has lifelong implications. If you find something, you need to be able to counsel the family appropriately.

Audience member: For neonate and older kids who have demonstrated venous sinus thrombosis, is it the opinion of the panel that heparin or some form of heparin should be the default therapy, and can you outline 1 or 2 reasons why any child should ever not be treated with heparin?

Dr DeVries: In our setting we always try to treat these infants because we do not feel like waiting for the propagation of the clot and maybe see an extension of the venous infarctions on the next scan, but you will hear more about it this afternoon.

Dr DeVeber: I suggest you read a paper by Mahendra Moharir. He has shown with protocol-based anticoagulant therapy that it is safe if you don't treat the big bleeds, and moreover that one-quarter to one-third of nonanticoagulated infants and children propagate their clot. And so when we look at recurrence and propagation, we're talking about probably the same thing.

PATHOGENESIS

Moderator: Zinaida Vexler, PhD, University of California–San Francisco, San Francisco, California

What Genes Are Implicated in the Pathogenesis of Stroke?

Frank Sharp, MD, University of California–Davis, Davis, California

Dr Sharp's talk focused on gene expression profiling of blood cells in ischemic stroke and the use of markers for the identification of ischemic stroke. Most RNA in the blood is produced by immune cells: leukocytes, neutrophils, and monocytes. The gene products of these cells provide insight into the immune response to disease, such as ischemic brain injury. RNA expression profiling of blood from rats revealed unique expression patterns within 24 hours of ischemic injury. This profiling was replicated in human patients and yielded an array of 58 proteins and 7 panels of proteins that are biomarkers for ischemic stroke. Additional studies yielded a 97-probe profile that is able to distinguish between subjects with ischemic stroke (86%) and control subjects who were healthy (84%), had vascular risk factors (96%), and had myocardial infarction (75%).

Several noteworthy genes identified in the profiling were matrix metallopeptidase 9, which degrades collagen; factor V, a coagulation cofactor; thrombomodulin, a thrombin cofactor; arginase 1, which promotes inflammation and fibrosis; S100A12, which may modulate neutrophil activity; carbonic anhydrase 4, whose function is not clearly understood; and chemokine receptor 7, which activates B and T lymphocytes. Additionally, specific genes expressed in different blood cells were identified with distinct subtypes of ischemic stroke. For instance, brain natriuretic peptide and D-dimer were associated with cardioembolic stroke, C-reactive protein was associated with large-vessel stroke, and homocysteine, intercellular cell adhesion molecule 1, and thrombomodulin were associated with small-vessel lacunar stroke. Although these specific bio-markers lack sufficient sensitivity and specificity to be used in clinical practice, a 40-gene profile differentiated between cardioembolic stroke and large-vessel stroke with greater than 95% sensitivity and specificity, and a separate 37-gene profile differentiated between cardioembolic stroke due to atrial fibrillation from that due to nonatrial fibrillation causes with greater than 90% sensitivity and specificity.

In addition to differentiating between subtypes of ischemic stroke, the expression profiling elucidated some of the various functional pathways at work in cardioembolic and large-vessel stroke. There were 503 genes identified to be uniquely associated with cardioembolic stroke, indicating involvement in the development of lymphocytes, inflammatory disorder, cardiomyocyte cell death, and phosphatidylinositol 4-phosphate modification. Additionally, cardioembolic stroke was associated with the canonical pathways of renin–angiotensin signaling, thrombopoietin signaling, nuclear factor-κB activation, cardiac hypertrophy, and B-cell receptor signaling. Five-hundred fifty-four genes were identified to be uniquely associated with large-vessel stroke, indicating involvement in T-cell and leukocyte development, inflammation, and invasion. Large-vessel stroke was associated with the canonical pathways of T-cell activation and regulation, chemokine receptor 5 signaling in macrophages, relaxin signaling, and corticotropin-releasing hormone signaling. Finally, 228 genes were common to both subtypes of ischemic stroke, indicating that both subtypes were associated with leukocyte and phagocyte development and movement, cardiovascular processes, nuclear factor-κB response element expression, and oxidative stress. Canonical pathways common to both subtypes include p38 mitogen-activated protein kinase signaling, Toll-like receptor signaling, interleukin-6 and −10 signaling, nuclear factor-κB signaling, B-cell receptor signaling, and NF-E2-related factor–mediated oxidative stress.

These gene profiles, when applied to the 30% of stroke patients in whom the cause of ischemia is unknown, can reclassify the cause as either cardioembolic or large-vessel stroke (probability >90%). To implement stroke prevention, the cause of stroke must first be established. Although the studies that produced this data must be reproduced with larger cohorts to validate the expression profiles, these data show great promise as a tool for determining the cause of stroke.

Neurovascular Niche

Eng Lo, MD, PhD, Harvard University, Cambridge, Massachusetts

Dr Lo discussed stroke as a comprehensive, integrated tissue response in which the entire neurovascular unit plays a role in evolution of tissue injury, rather than just neurons or blood vessels. The neurovascular unit consists of endothelial cells, vascular smooth muscle, astroglia and microglia, neurons, and associated matrix proteins. He specifically discussed active cell death mechanisms, ways of targeting the neurovascular unit, and transitioning from injury to repair after stroke.

During ischemic brain injury, 3 fundamental mechanisms can lead to cell death: excitotoxicity and ionic imbalance, oxidative stress, and apoptotic-like cell death. These mechanisms mediate injury in neurons, glia, and vascular elements and affect the function of mitochondria, nuclei, cell membranes, endoplasmic reticula, and lysosomes at the subcellular level. Neurons and oligodendrocytes seem to be more vulnerable to cellular death mechanisms than do astroglial or endothelial cells. After the onset of ischemic injury, ionic imbalance can result because of loss of energy stores. This energy loss can also cause the release of neurotransmitters and inhibition of their reuptake, which results in an excessive presence of neurotransmitter and, ultimately, excitotoxicity. Oxidative stress and damage occur during and after reperfusion, possibly due to excessive superoxide production in mitochondria. High calcium, sodium, and adenosine diphosphate levels in ischemic cells have been shown to stimulate excessive mitochondrial oxygen radical production. Although membrane integrity loss and organelle failure are prominent ischemic cell death mechanisms, research has also shown that apoptotic-like pathways are also present. These pathways include caspase-dependent as well as caspase-independent mechanisms.

Although understanding cell death mechanisms is important, clinically targeting individual pathways has proven to be difficult, as the group of cell death mechanisms contains redundant and overlapping features. The concept of the neurovascular unit includes endothelial cells, astrocytes, and neurons as well as the extracellular matrix and emphasizes the dynamic nature of signaling between vascular, cellular, and matrix components. Finding ways to target the neurovascular unit and to protect the cell-matrix and cell–cell signaling that maintains neurovascular homeostasis may prove to be a more fruitful clinical enterprise. Two main protease systems have been identified to this end: plasminogen activators (such as tissue plasminogen activator) and matrix metalloproteinases. To date, tissue plasminogen activator has been used for reperfusion therapy in stroke patients, and important links between plasminogen activators, matrix metalloproteinases, edema, and hemorrhage after stroke have been identified.

Most molecular targets have a biphasic role in stroke pathophysiology. In the acute phase, the targets mediate injury, and in the recovery phase, the targets contribute to neurovascular remodeling. Dr Lo suggested that this transition from the acute to the recovery phase is important to understand and may be key to the translation of treatments from experimental models to viable clinical therapies. Understanding, for each molecular target, how, when, and where the switch from injury to remodeling occurs; what neuronal, glial, and vascular cells are involved in the switch; and how the transition is regulated will allow researchers to optimize treatment to block the target without interfering with recovery. Finally, Dr Lo mentioned some of the elements that have been found to interact with this process, such as N-methyl-D-aspartate signaling, which has both beneficial and deleterious effects; glial and matrix scars, which may impede neuronal rewiring and recovery; and high-mobility group box 1 proteins, which contribute to neurovascular remodeling.

Inflammation and Stroke

Zinaida Vexler, PhD, University of California–San Francisco, San Francisco, California

Dr Vexler's talk focused on the role of inflammation in stroke, particularly in the poststroke cellular environment. She began by discussing communication, or "cross-talk," between the brain and the peripheral environment. After stroke, neuronal damage and the ensuing released cytokines and chemokines are biochemical indicators of damage to the site of infarct. In addition, activation of the complement system; release of oxidative products and matrix metalloproteinase enzymes 2 and 9, which degrade portions of the extracellular matrix; and other disruptions of the extracellular matrix contribute to local inflammation. Studies have shown that inhibition of the matrix metalloproteinase enzymes can protect sites from damage caused by inflammation, but only when inhibited early. Inhibiting these enzymes at late time points suppresses neurovascular remodeling, increases infarct volume, and retards behavioral recovery.

The context in which a cell or cytokine is functioning has a great impact on its effect. For instance, microglial cells and macrophages have historically been considered detrimental to recovery; there is strong evidence in adult stroke models to support this belief. However, microglial cells may play an important role in neurogenesis. Microglial cells primed with interleukin-4 have recently been shown to protect against global ischemia, support neurogenesis, and promote angiogenesis. Additionally, depletion of a microglial pool has been shown to worsen injury caused by stroke. On the basis of analysis by flow cytometry of CD45 and CD11b, most macrophages in the brain 24 hours post stroke are microglial cells, rather than monocytes. Neutrophils are noticeably absent. Tumor necrosis factor (TNF)-α is generally considered a contributor to inflammation and injury. However, many cytokines—including TNF-α—are pleiotropic, and their action depends on the receptor with which they are interacting; these signaling molecules may in fact have opposite effects on their targets when bound to different receptors. Cell origin also matters. When TNF-α is produced in microglial cells, it functions as a protective cytokine, but when produced in monocytes it exacerbates injury.

Inflammation is also a significant factor in neonates. High levels of interleukin-1, −6, −8, and −12 have been associated with abnormal developmental outcome. In animal models of

neonatal stroke, more than three-quarters of genes that are induced early after hypoxic ischemia are part of the inflammatory response. In cerebral ischemia, these factors—microglial activation, cytokine signaling, leukocyte adherence, communication across the blood–brain barrier—have been shown in the literature to differ between adult and neonatal stroke. In particular, the effect of inflammation on the permeability of the blood–brain barrier after stroke is significantly different in neonates than in adults. In neonates, the tight junctions seem to be more preserved in immature rat models, resulting in less leakage into damaged tissue. Therefore, not only may the components of local and systemic inflammation not be as tethered as previously thought, but this knowledge also influences decisions regarding drug therapy in neonates—drugs may simply not be able to access their target tissues.

The data set regarding inflammation in neurogenesis and repair following neonatal stroke is small. Early studies in the hypoxic ischemia model showed that there is a change in microglial activity and there is a protective effect—consistent with stem cell activity—but the mechanisms for both of these actions are not yet understood. A later study, using labeled stem cells, showed that the administered stem cells were present in the brain for a long period of time (as visualized in MRI). This may develop into a tool to visualize neurogenesis and repair.

What is currently understood is that a number of differences exist between adult and neonatal stroke with regard to inflammation. As previously discussed, the blood–brain barrier is relatively preserved in neonates, rather than acutely disrupted as in adults. Neutrophil extravasion is significantly less in neonates, and monocyte extravasion is delayed compared with adults. However, where microglial activation is gradual in adult stroke, the process is immediate and rapid in neonatal stroke. Finally, apoptosis is a more major component of the inflammatory process in neonates than in adults. Although the inflammatory response is an important component of the body’s response to an infarct and has a number of negative and damaging effects, recent data show that in the long run, inflammation can be used as a tool to effect positive outcomes.

Dynamic and Structural Formation of Thrombus

Patti Massicotte, MD, University of Alberta, Alberta, Canada

Dr Massicotte discussed concepts in the dynamic and structural formation of a thrombus, the inciting event of arterial ischemic stroke in children and in adults, and differences in thrombus formation in children. Her talk highlighted the involvement of the major components of thrombus and their interaction and then presented some unique challenges for pediatric stroke in the future.

Hemostasis is a normal process that protects the integrity of the high-pressure closed circulatory system; this is separate from vascular damage. Vascular damage is a result of pathological processes and results in the recruitment of platelets. The coagulation system is activated by tissue factor, which begins the clotting process and results in the formation of fibrin. In normal situations, regulatory mechanisms prevent thrombus from forming, but in pathological processes these mechanisms are overwhelmed and thromboses develop.

Thrombosis is the inciting event in arterial ischemic stroke in children. Local blood flow through the cerebral artery may be decreased or absent, which results in focal ischemia. Because of poor collateral blood flow in the brain, infarction occurs if the block in the thrombus is not removed. Platelets and fibrin play a major role as components of hemostasis and thrombosis. Red blood cells are seen in clots, but the red cells are involved because they get “caught,” rather than by active involvement; in contrast, platelets and fibrin are active players. Normally, platelets exist in a resting state and become activated because of a number of different chemicals or agents, by vascular damage, by exposure of collagen, or by tissue factor. Upon activation, platelets express a protein called P-selectin. Platelets also secrete a number of agents, which ultimately allow adherence to an area of vascular damage. Until 15 or 20 ago, the role of platelets was not recognized. It was thought that platelets had no role in the blood other than to circulate, but it is now recognized that a number of receptors on platelets allow them to interact with other platelets and with areas of vascular damage to form thrombi (eg, the protease-activating receptor-1, which is activated by thrombin, and the glycoprotein 1B95 receptor, which interacts with von Willebrand factor, which will have already settled on the area of damage in the vessel). The glycoprotein 6 receptor directly interacts with exposed collagen in the damaged endothelium and the adenosine diphosphate receptors P2Y1 and P2Y12. Platelets also have signaling networks. When the proteins in these receptors interact, signaling occurs either from the outside in or from the inside out, which allows the platelets to react. In addition, platelets are thromboregulated. They circulate in the blood, and if activation continues after a plug is formed, that is pathological. The endothelium provides secretion of substances that keep the platelet in the resting state, such as nitrous oxide and prostacyclin. When platelets are stimulated they produce substances such as adenosine diphosphate that feed back and cause the activation of more platelets; however, CD39, which is an ectonucleotidase that exists on the exterior of the endothelial cell, inactivates adenosine diphosphate and so can stop production of additional adenosine diphosphate and further platelet activation.

Coagulation is initiated by tissue factor. Until approximately 5 years ago coagulation was considered in the absence of cellular components, but it is now recognized that coagulation has important cellular components that interact. Tissue factor on tissue factor–bearing cells, such as monocytes, macrophages, and neutrophils, or tissue factor–bearing microparticles, which are particles that are exuded from cells, interact with activated factor VII, one of the proteins in the coagulation pathway, producing factors IX and X. When this happens there is a small burst of thrombin, factor IIA, which is the most powerful protein in the coagulation pathway, and although thrombin may be produced on the surface of a platelet, there are some animal data to suggest that other membranes may be involved in this reaction. The small amount of thrombin produced activates factor VIII and factor IX. The platelet also becomes activated, and there is subsequent amplification and propagation of thrombin production; this reaction occurs repeatedly and produces large amounts of thrombin. Whereas in normal situations regulatory mechanisms exist, in pathological situations the regulatory mechanisms become overwhelmed, large amounts of thrombin are produced, and thrombi are formed.

Regulation of coagulation is complex. This requires termination of thrombin production, elimination of the clot, and stabilization of the clot, all 3 of which occur simultaneously.

Inhibitors—including proteins such as tissue factor plasminogen inhibitor, which inhibits clot formation; anti-thrombin 3, which plays a major role in subduing activated thrombin; and proteins C and S, which are involved with inhibiting coagulation—are also important. To eliminate the clot, tissue plasminogen activator activates plasminogen, which then degrades the fibrin clot. Stabilization of the clot occurs through factor XIII, thrombin activatable fibrinolytic inhibitor, and plasminogen activator inhibitor-1; α-2 antiplasmin also plays a role in stabilization of the clot. In normal situations, a clot forms, but thromboregulation ensures that the clot is controlled.

In the event of an injury to a vessel wall, the first agents that arrive to attempt to seal the vessel and to repair the damage are platelets, which are activated via 2 different and independent pathways—through collagen and through tissue factor, either within the vessel wall or circulating tissue factor. After resting platelets are activated, tissue factor turns on coagulation. Thrombin is then produced and interacts with protease activating receptor-1 on the platelet. Activated platelets not only cause further activation of platelets but also produce serotonin, adenosine diphosphate, and thromboxane. In the collagen pathway, a von Willebrand factor circulates and binds to collagen that has been exposed in the damaged vessel; platelets bind to the von Willebrand factor via glycoprotein 1895. Platelets also interact with collagen directly through glycoprotein 6 and some involvement with the integrin α2β1, which is also found on resting platelets. Both glycoprotein 6 and α-2, β-3 result in more activated platelets, which then results in adhesion and secretion. When the endothelium is damaged it produces a protein, disulfate isomerase, which then interacts with platelets and also causes activation of the α-2β, β-3 protein. When platelets adhere to the vessel wall because of protein activation, there is a conformational change in the integrin or the protein, which allows it to combine with fibrinogen under low shear stress situations or with von Willebrand factor under high shear stress situations. In this way further platelets are recruited, which interact with each other within the thrombus itself.

In certain pathological conditions that do not cause disruption in the endothelium, how is tissue factor exposed to participate in thrombus formation? As previously mentioned, P-selectin—a marker of activated platelets—is present. Micro-particles containing tissue factor also circulate within the blood, but recent studies show that this tissue factor exists in an encrypted form. If this tissue factor were activated, these microparticles would stimulate coagulation continually as they circulate. When the endothelium is damaged it produces protein disulfate isomerase (also produced on activated platelets), and this protein is responsible for altering disulfide bonds within the encrypted tissue factor, allowing microparticles to be activated and participate in thrombus formation. Additionally, these microparticles have a ligand for P-selectin—P-selectin glycoprotein ligand 1. This allows the microparticles to interact with activated platelets and continue with clot formation. These microparticles have been associated with other pathological conditions, such as paroxysmal nocturnal hemoglobinuria, and with cancer, and some studies have implicated these microparticles in adult stroke.

In summary, thrombus architecture differs depending upon shear forces, blood flow, blood turbulence, and blood platelet counts. However, an extremely important component of the discussion—which has been repeatedly identified thus far—is that children are not just small

adults. Within their hemostatic systems there are a number of differences, and these differences may play a crucial role both in formation and in structure of thrombus. Several differences have been identified thus far in children. First, although little platelet research has focused specifically on neonates and children, neonatal platelets are hyporeactive, so this may speak to a difference in membrane proteins in these cells. Next, there are a number of differences in coagulation in pediatric patients. There are decreased levels of the vitamin K–dependent factors: factors II, VII, IX, and X. This means there are differences in the ultimate composition of the thrombus. In addition to decreased levels of vitamin K–dependent factors, thrombin is decreased in pediatric clots along with α-2 antiplasmin, whereas plasminogen activator inhibitor levels are increased. The inhibitors antithrombin, protein C, and protein S are also at decreased levels in the neonatal period, increasing to adult levels over time, which may play a role in the formation of thrombus. During elimination of the thrombus, plasminogen is decreased in children compared with adults, and tissue plasminogen activator is increased, although the role of this shift has not been clearly delineated. Differences in vessel walls have been identified in neonatal animal models and may translate into differences in children where there are increased glycosaminoglycans, the block of heparin molecules that are seen within neonatal vessel walls, which again may translate into differences in formation of thrombus.

Obviously, hemostasis is necessary, as there will always be vascular disruptions that require repair. Thromboregulation is present in normal situations so that pathological processes do not override the system and result in thrombosis. Architecture of formed clots is dependent upon a number of factors; developmental hemostasis is an area in which much work remains to be done. Challenges for the future include answering a number of questions regarding hemostasis and thrombosis, addressing developmental differences in neonates in children, and determining upon which membrane coagulation occurs. Data from animal studies show that this may include membranes other than those on platelets. All of these unanswered questions are very important and are going to translate into either the design of new antithrombotic agents or a change in use of preexisting antithrombotics and anticoagulants for prevention and treatment of stroke in children. All of this knowledge ultimately needs to be translated into multicenter clinical studies to look at safety and efficacy of prevention and treatment.

Neuroimaging After Stroke

Michael Rivkin, MD, Harvard University, Cambridge, Massachusetts

Dr Rivkin discussed new developments in neuroimaging and their effect on the study and treatment of children with stroke. His presentation was organized around 4 main points: the definition of nervous system plasticity, evidence of plasticity found in typical central nervous system development and how it differs from adults at the time of stroke, the association of central nervous system plasticity with experience in the real world, and the effect of stroke on central nervous system plasticity.

Plasticity is the ability of the central nervous system to alter its structure or its function in response to a persisting influence to do so. This can take a number of forms. One form is engagement in cognitive activity, such as learning, memory association, or memory

formation, particularly mnemonic encoding and mnemonic retrieval. A second form is training-responsive plasticity; this revolves around motor activity and can be best characterized by the ability to learn complex motor movements in response to practice. Structural and functional attributes accrue to the cortex that is involved in the practice. Last is response to injury. The question is, What does the central nervous system do endogenously in response to an injury like stroke, but also in response to relevant injuries such as head trauma or hemorrhage, and what can be used as leverage in terms of practice or in afferent stimulation to counteract that response?

The context at the time of the injury in children is very different from what is found in adults. The curves of synaptogenesis and synaptic pruning in children were first plotted more than a decade ago; these curves include the striae cortex, the visual cortex, and the auditory cortex. In the striae cortex, a maximum level of synaptogenesis is obtained at approximately 9 months of age, after which there is a period of slow decline to a final number documented in late adolescence. In the auditory cortex, there is a more biphasic program of development, in which a maximum is achieved at about 7 months of age and another maximum achieved at about 3 years of age, again, followed by a steady decline. However, in the prefrontal cortex the increase is delayed and achieves a maximum only at 3 years within a steady program of decline. This was the first documentation in humans of a difference in the spatial display of synaptogenesis and synaptic pruning and within that spatial difference a temporal gradient of when it occurs.

More recently, it has been discovered that the brain is not of uniform thickness in childhood but varies from place to place; thickness of gray matter varies anywhere from 1.5 mm in the occipital poles to 5.5 mm in the superior convexities. Although these measurements are dynamic, as thickness changes over time, the trend is toward a gradual thinning across the brain with the exception of the pericentral regions around the sylvian fissure, which demonstrate an increase in thickness over time. There is an inverse relationship between cortex thickness and performance on the Wechsler Intelligence Scale for Children vocabulary subtest, observations of which were extended by the Brain Development Study group, a multicenter observational study of brain development in children using cognitive data as well as detailed neuroimaging. In terms of overall volume, total brain volume remains about constant during this period, but gray matter declines and white matter rises.

The best model to demonstrate how brain volume interacts with experience is that of the musician—we ask whether there is a difference between the regional volumes of trained musicians and nonmusicians. According to initial images, the answer is yes; the regions of sensory motor function in the primary cortex, along with the inferior temporal gyri, and the left prefrontal cortex in the inferior frontal gyrus have larger volumes in musical adults. However, this leaves the question: Does music increase these regional volumes or do people with regionally increased volumes in these areas tend to migrate toward music? This question was next investigated in children, looking at those with no prior musical training. Again, areas of increased volume were seen in the primary motor area, in the primary auditory area, and in the corpus callosum in children who were given musical training. Additionally, there was a direct linear correlation between the amount of regional volume increase and the ability to perform on complex motor task tests.

Using diffusion tensor imaging, this work has extended now to white matter; in a study of adult musicians, professional versus amateur, matched for age, sex, and socioeconomic status, white matter organization in different regions of the brain was examined and showed greater fractional anisotropy in the internal capsule at the midpoint in professional musicians. In addition, there was a clear, linear relationship between the number of reported practice hours and the height of the fractional anisotropy. A similar relationship was noticed in the isthmus of the corpus callosum.

There is now a dynamic picture of cortical synaptogenesis and pruning leading to different thicknesses throughout the brain and changes in white matter microstructure. To that dynamic picture, arterial ischemic stroke adds an additional dimension, with the expectation that structural and functional secondary effects will be seen not only at the site of the primary infarct but also at remote sites that have reciprocal connections with the affected region of stroke and that would be reflected in some kind of abnormal developmental outcome. Clinically this holds true, and through the use of imaging researchers can understand why that is true and how the injury can be prevented or attenuated. Neuroimaging will allow researchers to look at typical development and to monitor the effect of environmental influence on development and abnormal development due to stroke and will likely prove valuable for monitoring the efficiency of treatments in the future.

Questions and Answers

Audience member: Dr Rivkin, do you know if anything is going to be lost in these developing children by constraining the hand that is developing typically but then being limited in terms of the activities? That is, if you're limiting your development on one side, is there something that could be lost?

Dr Rivkin: Just as the imaging has demonstrated the dynamic nature of development, one wonders about what the effect of constraint might be on the constrained limb. Very few studies have been done in children, but the functional studies using constraint-induced movement therapy have shown a lasting beneficial effect in the affected arm of children who have received the therapy without any evidence of a negative effect in the arm that was constrained. However, the program is different in most studies in children. In adults, the program consisted of laboratory-based constraint-induced movement therapy for 3 hours a day, but beyond that the adults were constrained using their more functional arm as the constrained limb for up to 90% of waking period during the day, and that kind of constraint therapy to my knowledge is not being done in children; it's a more abbreviated form of therapy that may range anywhere from minutes per day to an hour or 2 hours a day.

Dr deVeber: Dr Lo, you showed us some very elegant studies about the inhibition of gliosis, specifically the HMGB1 studies. Is there a timing issue in those experiments that might enable us to understand when we need to manipulate gliosis?

Dr Lo: The answer lies in inflammation, which can be construed as the beginnings of wound healing, tissue repair. So it's the transition from initial injury to repair, and as far as I know we don't know when these transitions take place, at least in the context of adult stroke. We probably can wave our hands and say that in the first couple of hours there is mostly injury,

but by about a week there may be repair and recovery, but when that transition takes place even by 2 days or 36 hours, we don't know, and that's an area for research.

Audience member: Dr Massicotte, do you think clots derived from fibrin and clots derived from platelets are separable in pediatric stroke? And looking into the future, how do you predict we might be able to tell whether the individual patient in front of us is having a problem with a fibrin-mediated process or a platelet-mediated process so we could best treat them?

Dr Massicotte: Dividing clots up into fibrin-based versus platelet-based may be challenging, and it's not only challenging from the basic physiological process, but it's also going to be challenging from the point of view of therapy, because certainly different antithrombotic therapy, antiplatelet therapy will target the platelets and anticoagulant therapy will target the coagulation system and production of fibrin. I'm not sure that it's going to be easy to tease apart. It may be individually based. It may be pathological-process based, and we don't know a lot about the endothelium and the vessel wall in children, and that plays more of a major role than we thought initially, much like platelets. They're very important players, and we're all convinced of that now, but the vessel wall has a huge role to play. I'm not sure, is the short answer, and it's interesting listening to the talks today because I don't know anymore whether anticoagulant therapy using different anticoagulants with different targets within the coagulation pathway is the way to go. Equally, I don't know whether antiplatelet therapy, which targets single receptors on the platelet, is the answer either; you saw the number of receptors. Platelets can sneak out and become active through another receptor, and it's going to be very challenging. I'm surprised that in the adult world, considering how challenging and complicated platelet interaction and thrombus formation and fibrin formation and coagulation are, that they have some good answers that a randomized clinical trial proved to be safe and efficacious.

Audience member: Dr Lo, how would you suggest tackling the challenging problem of determining how neurons and glia and everything interact during the pathogenesis of stroke, because my laboratory focuses mostly on neuronal cell death. How can you put everything together?

Dr Lo: Science traditionally is reductionist, so we try to break it up into bitable chunks. Having cell models or even animal models where we focus on specific steps is probably OK, because that's the way we're going to make headway, but in the end putting it all together is complicated. The in vivo imaging that has come to bear recently, especially with optical imaging tools where you can see these cells change in real time, might give us a leg up on this problem, but at the end of the day your question remains a good one but a difficult one to answer, how to parse out the different steps and then put it all together at the end for a drug.

CURRENT MANAGEMENT AND THERAPIES

Moderator: E. Steve Roach, MD, Nationwide Children's Hospital, Ohio State University, Columbus, Ohio

American Heart Association Guidelines

E. Steve Roach, MD, Nationwide Children's Hospital, Ohio State University, Columbus, Ohio

Dr Roach reviewed the current American Heart and Stroke Association guidelines. These guidelines are intended to cover a broad view of what is important for diagnosis and for treatment. For reference, a class I guideline is one for which there is compelling evidence or general consensus in favor of the action, class III guidelines are those for which there is compelling evidence that the action is harmful, and class II guidelines find a "middle ground" of sorts. Evidence for these guidelines is also coded; evidence ranges from level A evidence, which comes from multiple randomized clinical trial (ie, very strong evidence), to level C evidence, which is based on consensus and not controlled trials. Recommendations directly pertaining to treatment of childhood stroke are briefly summarized below from the original publication; the full list of recommendations is published by the American Stroke Association in *Stroke*.[7]

Management of ischemic stroke in children with sickle-cell disease should include prevention and/or correction of dehydration, hypoxemia, and hypotension; transfusions to reduce sickle hemoglobin; and prevention of iron overload and may include consideration of hydroxyurea treatment. Arterial dissection may be treated with low-molecular-weight heparin, warfarin, or an antiplatelet agent. Surgical procedures could be considered when optimal medical therapy fails. In children with stroke and heart disease, therapy for congestive heart failure should be provided and cardiogenic embolism prevented. Congenital heart lesions should be repaired and atrial myxoma should be resected.

Patients with arterial ischemic stroke and migraines should be evaluated for other risk factors, and individuals taking oral contraceptives may be advised to change forms of birth control. Tryptan agents may need to be avoided in children with known vascular risk factors and prior cardiac or cerebral ischemia. The underlying condition for a treatable stroke risk factor in a child who has had a stroke should be addressed. Iron deficiency, poor diet, lack of exercise, oral contraceptives, and tobacco use may need to be addressed in patients with stroke. Patients with nontraumatic brain hemorrhage should be evaluated for other risk factors, and coagulation factor deficiencies and vascular anomalies should be corrected.

Children with cerebral venous sinus thrombosis should receive supportive measures that include hydration, seizure control, and regulation of intracranial pressure. A complete blood count should be taken, and any infection should be treated with antibiotics. Supportive therapy should also include fever control, proper oxygenation, control of hypertension, and maintenance of normal serum glucose levels. It may be useful to treat anemia.

Low-molecular-weight heparin may be used for anticoagulation in children who are at risk of recurrent cardiac embolism, stroke, and hypercoagulable states. Warfarin is also a reasonable choice for long-term anticoagulation therapy. Aspirin (3–5 mg/kg/d) can be used for prevention of secondary stroke when the primary infarction is not due to sickle-cell disease and when the risk of recurrent embolism is low and no hypercoagulable disorder is present. This dose can be reduced if side effects occur. Tissue plasminogen activator can be

used in some children with cerebral venous sinus thrombosis but is not currently recommended for arterial ischemic stroke.

Enhancing Cellular Survival: Acute Neuroprotection

Rebecca Ichord, MD, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Dr Ichord began her presentation by reviewing the pathogenesis of stroke, as seen in the clinical arena. Children who have a stroke often have a condition that puts them at risk, such as heart disease, unidentified cerebrovascular disease, or simply being a newborn, and experience an inciting event or new condition, such as vascular trauma, infection, or birth. These then combine to produce a pathophysiological event of thrombosis, embolism, and critical hypoperfusion, which leads to the focal ischemic event. At the vascular physiological level, there is some degree of reperfusion and flow redistribution in the vasculature. This evolves over minutes and hours, and even days. When considering cellular processes, the cellular injury occurs in a very dynamic manner: Some cells die, whereas some cells are injured and are dysfunctional for a period of time. Some cells interact at a system level, although the system is now dysfunctional. All proceed with a reaction to the injury, not only in circulation with flow redistribution but also at the level of synapses and transsynaptic events, where there may be recovery of function in a cell and recovery of function in a system or in a circuit. Ultimately, the hope is that the combination of cellular reorganization, functional plasticity, and rehabilitation will provide a postinjury steady state with some degree of functional recovery. At any place in this process there may be opportunities for neuroprotection.

In the developing brain, cell death naturally occurs via apoptosis. However, in the presence of various injury mechanisms, such as those that occur in ischemia, this leads to ischemic necrotic cell death and systems interruptions that can result in transsynaptic cell death due to various interruptions in the connectivity of the system. In this case, as has been previously mentioned, it is important to consider how to assist perfusion and how to manage thrombosis and hypoperfusion. Initially, neuroprotection focuses on the area of infarct and the penumbra that is being salvaged; the goal is to prevent injured cells from dying and to help cells and the injured system to recover. First and foremost, the most basic measures must be taken—promoting oxygenation and cerebral perfusion by laying a child flat, regulating temperature and glucose, and detecting and treating seizures. Unfortunately, many breakthroughs in neuroprotection discovered in the laboratory, such as high-dose albumin or free radical scavengers, have not translated successfully to the clinical setting. In the past few years, the focus of protection has shifted from the individual dying cells to the larger neurovascular unit. This includes not just the cells fixed in the tissue but the circulating cells as well. This interconnected network is essential to maintaining viability and function in response to injury. Although these complex interfaces pose great challenges to understanding and treatment, they also present great opportunities, and any consideration of focused, targeted intervention must be placed in the context of the temporal spectrum of injury and recovery in this complicated environment.

Moving forward, it seems to be important to target injury mechanisms that extend over a greater time period, because there is no way to treat stroke outside the laboratory setting

immediately after injury. Rather, targets for protection and treatment need to be available over an extended period, and protection methods need to address multiple injury mechanisms and multiple cell types. The immature brain may provide an advantage for these efforts, as it is poised to be adaptive and may naturally provide a larger window of time for treatment. One of the most promising treatments of the moment is controlled hypothermia, which is currently being tested in adults and, if successful, should be adapted for children. The most important point is that neuroprotection will not be accomplished by just one treatment or just one drug but rather by cocktails of interventions that provide multiple ways to assist the injured brain.

Constraint-Based Therapy and Rehabilitation

Edward Taub, PhD, University of Alabama, Birmingham, Birmingham, Alabama

Dr Taub addressed a new approach to rehabilitation developed in his laboratory called constraint-induced movement therapy. Although its procedures are relatively simple, constraint-induced therapy has been found to produce large improvements in the ability to use an extremity affected by cerebral palsy, by stroke—in children and in adults—and by other disorders consequent to substantial injury to the brain. This technique involves intensive physical therapy and training of the affected limb, such as an arm; restraint of the less affected limb; and a “transfer package” of behavioral techniques that help the patient translate therapeutic gains to everyday life situations. These techniques work because of at least 2 mechanisms: massive use-dependent brain reorganization, and overcoming of learning nonuse. Constraint-induced therapy has been applied to a number of conditions. The research was begun on upper extremities in adults with stroke; was expanded to cerebral palsy, where there is also a pediatric constraint-induced therapy procedure; and was then expanded to adults and children with traumatic brain injury. It is now being used in adults with multiple sclerosis. Additionally, the paradigm has been applied to the lower extremities, first with stroke, spinal cord injury, and hip fractures. Lower extremity work has not been conducted in children, although it will begin soon.

In pediatric constraint-induced therapy, the main modification from adult constraint-induced therapy is that children’s attention shifts must be accommodated. This therapy is conducted 3 hours a day for 10 to 15 consecutive days, depending on the severity of the deficit, and the less-affected extremity is restrained 24 hours a day. In an upper extremity study, the treatment group of children showed a 425% increase in use of the more affected arm versus the less affected arm, although this was reduced by approximately 30%, to just under a 300% increase in use, 6 months after treatment. With aggressive use of the behavioral technique transfer package, 6-month retention of use is now near 100%. In the control group, traditional occupational and physical therapy affected no change, but after 6 months this group crossed over into constraint-induced therapy and also showed an increase in use of the more affected limb.

As previously mentioned, one of the mechanisms involved in improvement of movement produced by constraint-induced therapy is use-dependent plastic brain reorganization. Study of this mechanism is a work-in-progress in children, but initial data agree with previous data from adults that show a large increase in gray matter on the contralateral side of the brain

and in sensory motor areas. Anterior motor areas show a large change in the ipsilateral cortex, and there is also an increase in the gray matter of the hippocampus. No change has been seen in control subjects.

In summary, constraint-induced therapy involves intensive training of an affected limb and restraint of the less-affected limb (more important in children than in adults) in conjunction with a transfer package of behavioral techniques that help the patient translate therapeutic gains to real-life situations. This therapy has shown that plastic change in the brain can be harnessed to produce therapeutic improvement in a condition once thought to be irremediable. Finally, and possibly most important, although it is common knowledge that the central nervous system produces straightforward behavior, it can have a profound reciprocal effect on the peripheral nervous system, which is constantly in the process of being modified and remodeled by environmental external influences.

CONTROVERSIES AND UNANSWERED QUESTIONS

Moderator: Gabrielle deVeber, MD, The Hospital for Sick Children, Toronto, Ontario, Canada

How to Treat Newborn Sinovenous Thrombosis

Mahendra Moharir, MD, The Hospital for Sick Children, Toronto, Ontario, Canada

Dr Moharir's talk focused on the clinical management of neonatal sinovenous thrombosis and on the challenges encountered when treating a newborn with sinovenous thrombosis. In particular, Dr Moharir addressed anticoagulation therapy, considered key for treating sinovenous thrombosis, and its safety in newborns. Additionally, he addressed concerns about appropriate length of treatment, if initiated, monitoring of a treated newborn, and concerns for patients who have not been treated with anticoagulation therapy. Last, Dr Moharir discussed the effect of anticoagulant therapy on long-term outcomes, in terms of both recanalization and clinical condition.

Sinovenous thrombosis is considered a hypercoagulable state, due to an imbalance between the coagulating system and the fibrinolytic system. This could be caused by a variety of factors but most likely in newborns is due to venous stasis and lower levels of natural coagulants such as proteins C and S and antithrombin 3. Ultimately, this results in obstruction to the venous flow and retrograde venous congestion. If this situation goes uncorrected, the capillary hydrostatic pressure increases and fluid is driven into the interstitium, resulting in venous edema and increased intracranial pressure. This can eventually progress to the point where venous capillary pressure exceeds arterial pressure, and arterial inflow reduction and regional ischemic infarction (or venous infarction) result. Typical targets for management include risk factors that predispose a patient to further clot formation, protection of the brain from the ill effects of the clot, and recanalization of the clot to alleviate the venous congestion. Methods of targeting the clot include antithrombotic agents, thrombolytic agents, and surgical or mechanical thrombectomy. The most common antithrombotics are heparin derivatives, vitamin K antagonists, thrombin inhibitors, and antiplatelet agents. The goal of using anticoagulants or antithrombotic medications is to

restore the balance between the coagulation system and the fibrinolytic system and to enable the body to dissolve the clot via fibrinolytic mechanisms rather than by clot lysis. There are currently no randomized trial results for treatment of neonatal sinovenous thrombosis. However, recent studies provide increasing data on the safety of anticoagulant therapy and data showing that neonates recanalize clots faster than older children. In contrast to American Heart Association guidelines, guidelines published by *Chest* recommend anticoagulation in all neonates without hemorrhage and, in cases of significant hemorrhage, no anticoagulation but monitoring for clot propagation.

When deciding whether to treat a child with sinovenous thrombosis with anticoagulant therapy, it is important to know whether intracranial hemorrhage is present and to determine how significant it is. However, what exactly constitutes significant hemorrhage in this condition is unclear. Also to consider are clot load, central nervous system mobilities that increase bleeding risk, and the overall clinical condition of the child. Whether or not anticoagulant therapy is initiated, follow-up on these children is of the utmost importance. The bleeding risk with unfractionated heparin is between 0% and 18% and with low-molecular-weight heparin is between 3% and 10%. It is important to avoid loading doses when initiating unfractionated heparin, because the surge may increase the risk of hemorrhage. Treatment duration is also different for unfractionated versus low-molecular-weight heparin, the former recommended only for a few days rather than the latter, which can be given over months. Vitamin K antagonists are not recommended in neonates because the plasma levels of vitamin K–dependent coagulation factors are physiologically decreased, and therefore the antagonist is less effective. Similarly, because of reduced plasminogen levels in neonates, plasmin production is slow, which reduces the effectiveness of thrombolytic therapy.

Treatment has to be tailored to individual patients. However, on the basis of the data currently available, anticoagulant therapy appears to be safe in the absence of intracranial hemorrhage and may even be safe in the presence of intracranial hemorrhage; however, studies to confirm that theory are essential. Low-molecular-weight heparin therapy is the mainstay of treatment of sinovenous thrombosis in neonates, but it is also vital to focus on neuroprotective interventions as well as management of associated risk factors.

Secondary Stroke Prevention in Childhood Arterial Ischemic Stroke

Heather Fullerton, MD, MAS, University of California–San Francisco, San Francisco, California

Dr Fullerton centered her presentation on how to prevent recurrent strokes in children, discussing not only the role of antithrombotics in the management of childhood arterial ischemic stroke but other treatment options for secondary stroke prevention. The goal of antithrombotic therapy is to prevent recurrent stroke, rather than prevent extension of the initial stroke, except in the case of basilar artery thrombosis, where propagation of the clot can block perforators to the brain stem. Of the 20% of children who will have a recurrent stroke, most of these will happen in the first 6 months to 1 year. Very few recurrences happen after 2 years, and these are primarily among children with arteriopathies such as Moyamoya disease. Although the literature provides little in terms of secondary stroke

prevention, in general there is a consensus that anticoagulation should be used for arterial dissection (although there is debate about whether this therapy should be used for intracranial dissection) or cardioembolic stroke, and aspirin should be used for all other types of stroke. However, these guidelines are based on weak evidence, so any number of questions remain, including the best antithrombotic for children and the proper time to begin treatment with anticoagulation therapy. Certainly, any antithrombotic therapy has risk, and the adult data show that whether the given treatment is aspirin or anticoagulation, the risk of hemorrhagic transformation is elevated. In addition, children typically have large-vessel strokes rather than lacunar strokes as seen in adults, so this also increases risk.

There are some relative contraindications to heparin use in acute stroke. The size of the middle cerebral artery territory considered too large for anticoagulation varies depending on the practitioner, but any very large middle cerebral artery stroke increases the risk of producing symptomatic hemorrhagic transformation due to acute anticoagulation. In the absence of imaging, the guideline is that weakness of the face, arm, and leg is indicative of a large stroke, because in this case a middle cerebral artery stroke will involve the internal capsule and the basal ganglia, or there is a combination of middle cerebral artery and anterior cerebral artery stroke. This should make practitioners cautious about starting anticoagulation, and if heparin is started it is important not to use a loading dose in order to avoid supratherapeutic anticoagulation. It is difficult to address whether antithrombotic agents improve outcome, as practitioners are unwilling to randomize children to placebo. However, on the basis of adult data and some limited pediatric data, antithrombotic agents seem to decrease the risk of recurrent stroke.

Clinical practice requires physicians to go beyond the evidence, because—as has been mentioned so many times previously—the evidence simply isn’t in place yet. If there is a recurrent ischemic event in a patient on aspirin, there are good adult data to suggest that adding Plavix has benefit over aspirin, and there is now cardiac literature that outlines dosing of Plavix in children. For a child who experiences ongoing events despite medical management, second-line therapies can be used. Surgical intervention to remove the web, stenting, and other endovascular options may help in the event medical therapy fails. Specific disease etiologies may require different treatment methods. For instance, an antithrombotic agent will not be helpful in the case of the hypoperfusion events of Moyamoya disease, and anticoagulation is considered too high-risk. Stents and embolization have been shown to be helpful in the case of arterial dissection. Intracardiac thrombi are typically treated with anticoagulation for several months or until the clot dissolves. These interventions should be reserved for cases where children are failing medical management, which suffices most of the time. Ultimately, it is one of the primary goals and responsibilities of the International Pediatric Stroke Study to work toward secondary stroke prevention trials in children so that better clinical decisions can be made and so that those decisions can be grounded in evidence-based medicine.

Does Hypothermia Have a Role in Treatment of Childhood Stroke?

Donna Ferriero, MD, University of California– San Francisco, San Francisco, California

Dr Ferriero debated the merits and sagacity of using controlled hypothermia as a treatment method for pediatric stroke. She introduced the discussion by stating that there are no trials and no controlled data on this topic at this time and that the current thinking is couched in examples from other populations and other disease paradigms. The best example of the use of hypothermia in treatment is neonatal hypoxic–ischemic injury; in this paradigm both whole-body and head cooling have shown efficiency. Additionally, as previously discussed, approximately 5% of the population diagnosed with hypoxic– ischemic encephalopathy actually have stroke. Meta-analysis of published trial data shows that cooling shows efficacy in reducing death or disability and that normal neurological examination also favors hypothermia for the hypoxic–ischemic encephalopathy population. However, several major concerns confound the decision-making process. First, the treatment population is ill-defined. The questions of whom hypothermia will benefit (neonates vs all patients), what types of stroke to treat with hypothermia, and precisely what the window of opportunity is are all unanswered. Children often take longer to present with clinical symptoms of stroke, but, as was previously presented, cell death is an evolving process in which recovery and regeneration take a long time. Identifying the window of treatment opportunity in this timeline is difficult. Additionally, it is not understood how long patients should be treated or how cool they should be kept during treatment.

Previous studies using hypothermia to treat cardiac arrest show that induced hypothermia is both safe and efficacious. Adult studies going back as far as a decade favored hypothermia based on 6-month outcome. Pediatric studies are now taking up the question of whether hypothermia is an effective treatment for childhood cardiac arrest, with promising initial results. A review of the cases in these studies shows that many of the causes of cardiac arrest were asphyxial, so they may provide hope that ischemic causes will respond in a similar manner. Two small completed prospective trials in the adult population show safety and feasibility, the Cooling for Acute Ischemic Brain Damage (COOL-AID) studies. COOL-AID 1 involved surface cooling for 12 to 72 hours as an adjunct to tissue plasminogen activator, and COOL-AID 2 involved endovascular cooling with induced moderate hypothermia for 24 hours as an adjunct to thrombolysis. Both studies showed that the techniques were feasible. There are also several other ongoing prospective clinical trials for adult stroke. The Invasive versus Conservative Treatment for Unstable Coronary Syndromes (ICTUS) study showed not only that tissue plasminogen activator with endovascular cooling was feasible but also that it was safe. One key point that has been made multiple times is that temperature regulation of children with stroke is of the utmost importance. Although hyperthermia is dangerous to the ischemic brain, prolonged dramatic hypothermia may also be dangerous, requiring very careful temperature regulation and monitoring if hypothermia treatment is attempted.

In sum, it is difficult to say what role hypothermia has in treatment of childhood stroke at this time. As with so many other questions in this field, further studies for this treatment in pediatric stroke are needed. Although adult studies seem to indicate that hypothermia is safe and feasible, the timing of treatment and which population should be treated are still not known.

Questions and Answers

Dr Kirkham: What worries me is that if you do constraint therapy to get a better motor outcome in the child in a developing brain you might redirect neurons that were going to be part of a child's cognitive development, relocate them for the motor site, and get a good motor outcome but at the expense of the cognitive outcome. Do you have any data on the IQ for the children with the constraint therapy?

Dr Taub: Cognitive delay, up to a certain point, does not predict treatment outcome. After all, we developed the therapy with monkeys. As to whether there is a trade-off between improved use of the arms and cognitive development, we do have some measures of cognitive development. We haven't noticed any deterioration, but we have not done an extensive study of the cognitive function, and so I can't give you a complete answer, but there's no effect on the DAISY2 or language as far as we can tell. We have tested language in adults and have seen no effect. In adults, there is an enhancement of linguistic ability, and we also see that clinically in children, but it is a question as to whether that's the constraint-induced therapy or the intensive social interaction that the therapy involves. But as far as we can tell, clinically there is no detriment to cognitive ability.

Audience member: For Dr Taub as well, you mentioned 10 to 15 days of consecutive constraint. How many sessions did the patients have to undergo, and how sustainable was that outcome?

Dr Taub: For 3½ hours a day, we worked with the parents for a half hour training them to be substitute therapists, but with the child we worked for 3 hours a day and for 10 to 15 consecutive days, consecutive weekdays, and whether it's 2 weeks or 3 weeks depends on the severity of the deficit. We have a grading system for severity of deficit based on active range of motion, which we measure before and after treatment, and we grade the severity of the impairment in those terms. And so for grade 4 and 5, the most severe strokes that we work with, it's 3 weeks, and 2 weeks for grades 2 and 3.

Dr Bernard: I'm wondering if you could comment about stem cell therapy as being a potential treatment in the future from 2 angles. Long-term do we think it's a viable alternative, but also currently some people are using that as a therapy on some patients, and I increasingly have families coming to me saying, "Should I do that, should I not?"

Dr Ferriero: We should just say "cell-based therapy," because we're dealing with a number of different types of therapies that are being made available to unsuspecting patients that have not been adequately tested in animal models. If ever there was a need for reverse translation, it would be to find out, for example, if you have cerebral palsy for 5 years because you had perinatal stroke and you put some cord blood into your body, what is that going to do to you aside from maybe making a few tumors here and there? So I think we are so far away from understanding efficiency of stem therapy. There are some beautiful papers most recently published from the Utrecht group on mesenchymal stem cells looking at efficacy. Without even repairing structure, they're getting beautiful effects on function. These are all encouraging data, but we are so early in the preclinical phase that we have to

hold fast with our patients and try to get them not to rush to certain states in the union or China.

Executive Summary of the Day

Dr Jerome Yager, MD, University of Alberta, Edmonton, Alberta, Canada

Dr Yager gave a closing talk highlighting major points of the day and reviewing points of emphasis. He began by reiterating not only that stroke is very common in childhood but also that childhood stroke is very different from adult stroke; the causes and recovery processes are different, which pose tremendous clinical challenges for diagnosis and treatment. A large delay in diagnosis occurs in the hospital setting, and practitioners need to look more aggressively at imaging specifically for stroke. Although there is very little evidence for overcoming so many of the treatment challenges, there are several expertbased management guidelines that focus on aggressively managing physiological homeostasis and using disease-specific management. Multiple speakers also emphasized the need to recognize the multiple predisposing factors, such as maternal, pregnancy-related, fetal, and newborn factors, which occur over a developmental process, making the ability to attend to those issues very difficult because the target is constantly moving. Future challenges are posed by the fact that these events occur over the developmental spectrum and are extremely heterogeneous. Unlike adult pathogenesis, which tends to be more consistent, childhood stroke has varying pathogenesis. It is important to identify which factors to concentrate on pathophysiologically; this will be key to any efforts at prevention. Rehabilitation such as constraint-induced therapy looks very promising, but continued investigations of prevention are also desirable, and based on the genetics presented there may be a number of biomarkers that will aid in those efforts.

Several themes were repeated throughout the day in terms of management of patients with stroke: careful management of thermoregulation—euthermia for now, although mild hypothermia is also a possible treatment modality—and prevention of hyperthermia, which is recognized as being detrimental. Also important are maintaining systemic blood pressure and glucose homeostasis and monitoring iron levels. The question of whether to anticoagulate was addressed several times, each time with the message of moderation in almost all cases. Anticoagulation can be an effective approach for preventing secondary stroke, but there is still a lack of understanding about which anticoagulants are best in children, which groups of patients will benefit, what the dosing of anticoagulants should be, and what the risks are for a patient with a large stroke. The current American Heart Association guidelines address many of the issues in management, acknowledging that so much of the thinking is based on consensus rather than evidence. This underscores the need for controlled studies to elucidate best-practice methods for diagnosing, managing, and treating childhood stroke.

Several speakers discussed the pathogenesis of stroke. A number of biomarkers and genes have been identified that can aid practitioners in determining the type of stroke and the underlying cause, which will help immensely with efforts to manage patients in a disease-specific manner. A discussion of inflammation highlighted that it is a bidirectional process: although inflammation is generally seen as detrimental, chemokines and other cell signals

can spur the recovery and regeneration process. A major point is that inflammation in children and neonates is vastly different than in adults, and specific investigation of the inflammatory process in pediatric models is necessary for furthering the understanding of the role of inflammation in stroke. As in inflammation, the process of thrombus formation requires a delicate balance. Upsetting that balance will result either in bleeding or in pathological clotting. This is also a point of which to be mindful during treatment; efforts to resolve a clot can overcorrect that balance and result in bleeding. How best to treat thrombus is an area in which, again, there are many unanswered questions that require further investigation.

Moving forward, it is important to identify clinical pathways for diagnosis and treatment and make them well known, not only to those interested in stroke but also in a much broader sense. Practitioners need to be pragmatic in their approach to treatment and management, to emphasize the ABCs and physiological homeostasis. There is also a need to identify specific cohorts for clinical trial rather than using a broad approach. Pediatricians need to advocate for therapies that work and to refine and combine those therapies, such as hypothermia and constraint-induced therapy. There is also a need to use imaging more aggressively to guide therapeutic approaches and to evaluate their success or failure. For research, multicentered collaborative approaches, such as the International Pediatric Stroke Study and other European and Australian studies, are the key to the future.

Future Directions: Panel Discussion/ Questions

Moderator: Deborah Hirtz, MD, Office of Clinical Research, National Institute of Neurological Disorders and Stroke

Audience member: My understanding is that protein S, protein C, and antithrombin are basically associated with venous infarct and that the phospholipid antibodies and the prothrombin gene mutations are associated more with arterial infarct in adults. Does that hold true for children?

Dr DeVeber: Yes.

Audience member: Another point in terms of biomarkers is that maybe we should emphasize family history for venous infarcts, because Leiden deficiency is pretty common in the population, and so if we have other adults who have deep vein thromboses that might be a warning sign.

Dr Roach: I would agree. Usually with these things you’re talking about venous thrombosis. One other point, though, is that when you have a venous thrombosis in the setting of factor V Leiden or one of the others you mentioned there are almost always multiple risk factors, so it’s a layering of things, and over the last few years we’ve grown more sophisticated in talking about risk factors as opposed to the cause, which implies there is one thing. So most of these things in isolation are fairly low-order risk factors.

Dr Kirkham: I don’t find very many children at all with protein S deficiency, but we have had one child recently with antithrombin 3 deficiency, and that child was known to have a

family history, so I very much emphasize that family history is very helpful. Protein C deficiency is a bit more common, and it's probably a risk factor for recurrence in venous stroke and possibly in arterial stroke. But the genetic markers are probably more fruitful. If you have to choose between exactly what you going to do, that is probably a bit cheaper and probably has a higher pick-up rate.

Dr Vexler: There is a very strong effort among many investigators here in this room to consolidate the knowledge and what we know, what we don't know about different types of brain injury in children, but from the bench side one more thing can be helpful in terms of biomarkers. So there are several clinical trials that are either on the way or shortly on the way. If by some kind of biomarkers additional information can be learned, based on adverse effect and association and the family history, there may be additional information that can be extremely important to put things in perspective.

Audience member: Would you comment on hypothermia in the diffuse hypoxic–ischemic encephalopathy that is seen with near drownings?

Dr Ichord: There are good pilot data to show that it is both feasible and safe. The example from the adult cardiac arrest studies is extremely compelling, and putting together the trial for post–cardiac arrest hypothermia in children, many pediatric intensive care providers were hesitant about having equipoise for doing that, so there are compelling data from the adult world as well as the neonatal world. It seemed very logical to extend this to the pediatric world, and we're hoping from the trial to get insights into the parameters of cooling and more data on predicting outcome and predicting which children may benefit and what we can do to add on to hypothermia. So the time was either now or never to do the trial. It's underway. It's about a year into recruitment, and we're going to start seeing the 1-year outcomes, so I think this will be an extremely fruitful dataset.

Dr Hirtz: Another topic that hasn't been mentioned is the use of hypothermia for traumatic brain injury, and there is a major NINDS-funded trial going on right now—called the COOL-KIDS trial—looking at hypothermia for traumatic brain injury. There was a pilot trial that indicated there might be very good efficacy for neuroprotection by the same group. On the other hand, there was also a recently published Canadian trial by Dr Hutchinson that used a shorter period, a 24-hour period, as opposed to a 48-hour period of hypothermia and a quicker rewarming period, which did not show benefit.

But in spite of that, the COOLKIDS trial is progressing with optimism, although it's difficult to recruit patients, and in the COOLKIDS trial the hypothermia is being used for 48 hours plus. It's used for 48 hours, and if the intracranial pressure is still high, it's used for longer. The rewarming period is slow. Hopefully we'll have results of that. It's expanding to international centers.

Dr Maria: I didn't want to pass up on the question of what each of you thinks that the greater membership of this society or child neurologists broadly can do to be more effective or most effective in helping move the field forward. Can you give us thoughts on what roles we should play, those of us who aren't immersed within the field? How can we in the community, broadly speaking, be helpful?

Dr deVeber: The most important thing that general pediatric neurology and this membership can do is to train more pediatric stroke specialists, make room for them, support them as young faculty, and thereby increase the very tiny number of stroke specialists who practice now. Probably the second part to that, or even in the absence of that, is to implement the guidelines that have been published as interim measures so that at least you're following the guidelines, and I'm basing that on the fact that stroke units in adults have been shown to be more effective than tissue plasminogen activator at improving outcome, and it's not the magic of the bed or the mattress. It's the specialized care that these patients get, and that is where the future is.

Dr Ferriero: I also would like to emphasize for people in practice to get out there and tell your colleagues in family practice and general pediatrics that you're there to help them increase their awareness of warning signs of stroke, and especially for the young infant, early handedness. We can do so much more if we can identify the children and provide rehabilitation therapy.

Dr deVries: Every newborn infant who comes in with neonatal seizures deserves to get an MRI and a magnetic resonance venogram because we see so many unexpected strokes or cerebral sinovenous thrombosis, and they would not be recognized without appropriate imaging.

Dr deVeber: Our responsibility also as pediatric neurologists is to protect our stroke patients from interventions that may not help and may hurt, and I'm specifically talking about very adventuresome intravascular techniques, which are sometimes called cosmetic arterial procedures. These could offer promise, but it's our responsibility to not be swayed by the keenness and the eagerness and the aggressiveness of some of the interventional colleagues who work a lot on adult arteries but not so frequently in childhood.

Dr Yager: What I'd like to see also is for the importance of early identification and diagnosis to penetrate the primary care community of pediatricians and family physicians. We talked about how the handedness question is often the forgotten issue in terms of development. It's not part of a normal well-baby aspect. Typically the screening on development isn't happening well beyond a year of age, so we need to establish a strong umbilical connection with the American Academy of Pediatrics and pediatric academic societies to get that educational message across.

Dr Ichord: I would echo that we neurologists are a very small group, and we need for the primary care providers, both emergency room and primary care pediatricians, to be eyes and ears, and I would echo a theme that the families bring up over and over again—that the families are better at diagnosing stroke than physicians. If the message is as simple as listening to the parents when they say, "I think my child is having a stroke," we may go a long way.

Dr Hirtz: We should also not give up on looking at strategies for neuroprotection. Our adult colleagues, for various reasons that have been described, have not had a lot of success despite enormous amounts of funding, efforts, and trials, but we have reason to think that perhaps we can succeed where they have failed even, and I do hope that people will continue

to think about research projects that will end up with phase 3 trials in neuroprotection in infants and children.

Audience member: I had a question regarding the panel's thoughts on the use of supplemental oxygen in the nonhypoxic, non–sickle cell population. I think the current guideline is that it's a level III recommendation that you not give supplemental oxygen. Yet intuitively it makes sense. Could you just comment regarding that recommendation and the rationale?

Dr Ichord: I tend to agree with your logic that when there is an area of ischemic brain injury, part of the resuscitation of that involves improving oxygen delivery, and at the moment it's true that we don't have evidence to say whether it's helpful. It's hard to imagine that it's harmful, and in a patient who is acutely neurologically impaired, there may be problems with their airway management or with their ventilation, and it's common practice in ICUs to use supplemental oxygen. The flip side of that coin is that overexposure to high levels of oxygen may be harmful, so the bottom line is that we don't know, and we need to keep an open mind about looking at safety as well as efficacy in all interventions. That first principle still pertains, ABCs, and if there is a compromise of A, B, and C, we should deal with those with the data that we have, but we still need to evaluate what is the right thing to do in terms of oxygen treatment.

Dr Ferriero: I strongly suggest that we be very temperate with the oxygen, because giving oxygen to failing mitochondria only creates more oxidative stress and free radicals, and we know that oxidative stress is a part of this problem. The other issue is that the brain is trying to respond with endogenous injury mechanisms, and one of those very strong responses is hypoxia-inducible factor. When hypoxia-inducible factor meets hypoxia it is upregulated and starts cranking out a number of growth factors and glycolytic enzymes that help to repair the brain. The brain is trying to help, so we have to be careful in our thinking about how much oxygen we want to give.

Audience member: Most of the genetic things we talked about today have to do with neutrophils, platelets, fibrin, and the coagulation cascade. In adult stroke there is evidence that if you look at genetic regulatory mechanisms of blood vessel structure, collagen in particular and mutations in genes that regulate collagen, it predisposes to vascular disease. Is there anything out of that work that we think is applicable to being a risk factor in the neonates?

Dr deVries: We have seen a number of children now who have antenatal bleeds with porencephaly and old clots in their ventricular system at delivery and sometimes even very extensive bilateral porencephaly, which were related to an A1 mutation. Others have seen this as well and have seen fetal hemorrhages presenting at birth with porencephaly once again. In children, presumed perinatal stroke with venous infarction that maybe calls for A1 should also be considered as an underlying problem.

Dr deVeber: There are cases now of *ACTA2* deficiency, which is a diffuse arteriopathy in childhood, and the evidence from young adults with dissection when there isn't clear trauma preceding it is pretty compelling that there are ultrastructural changes in the skin, and

therefore likely in the cerebral arteries, that are congenital and on the spectrum with that type of collagen problem.

Audience member: Given the similarities of pathogenesis with migraine and stroke and the fact that migraine with aura seems to predispose to stroke later on, what should our posture be about these migrainous patients with focality?

Dr Ichord: Children who look like they have a complicated migraine are among the most difficult emergency room patients because they may resolve their deficit fairly quickly and their headache looks very much like a migraine, and the problem we have is distinguishing them from a true stroke. And as we've heard, many children who have a true stroke in fact have a migraine at the onset of their symptoms. So one can choose to be maximally aggressive and admit and evaluate such patients as though they were an adult with a transient ischemic attack, where the approach is to be maximally aggressive and evaluate such patients for stroke. Until we have more data that help us to distinguish between a patient with a simple symptomatic or complicated migraine and a patient who has just had a transient ischemic attack that is accompanied by a headache close examination is necessary. In children with deficits which may be vascular territory deficits (eg, face, arm and leg with aphasi or aphasia with sensory motor findings), the adult literature indicates that the more pronounced and bigger the deficit, the more it matches a stroke distribution, the more concerned we should be that the child actually has a vascular lesion. But until we have more data that separate the child with his first or first complicated migraine from the child with true vascular disease, we have to make the best decisions that we can with the individual we have in front of us and the resources that we have to evaluate them.

Dr Roach: Just when you thought that this whole syndrome of familial complicated migraine couldn't get more complicated, there are at least 3 defined genes for that now, and traditionally it's been a case of "you're going to get better but you're going to have repeated attacks," but now there are several case reports and a series in the literature where these kids have strokes. So practically speaking, one of the things that people often overlook is the family history, and it's not always hemiplegia. It's probably misnamed. It ought to be named *familial complicated migraine syndrome because* you'll see people who have hemiplegia, and then you'll see a first-degree relative who has some other deficit, and that these people are worth teasing apart from the others because you probably don't want to have them on certain forms of therapy for migraine. That's probably true of all people with complicated migraine. Also, there is at least some anecdotal evidence that for familial complicated migraine, things like calcium channel blockers are likely to work better than some of the other migraine therapies, so taking a good family history is one just practical point.

Dr deVeber: I would agree with what has been said, but my experience on this is that I cannot tell the difference. In an older child who tells you about the progression of over 5 minutes' spread, then maybe you have hope, but I think generally if there is a hemiplegia, you require MRI with diffusion and while you're at it a magnetic resonance angiogram, and if both of those are negative, and the deficit has persisted, then you can be more confident. Another positive test sometimes is an EEG, which shows hemispheric delta slowing at the time of the deficit in the presence of a normal MRI.

Audience member: Do you anticipate that you will issue any kind of recommendations that we could use, as practicing child neurologists, to help us move forward in advocacy, specifically around the idea of being able to provide rehabilitation such as constraint-induced therapy, and the issue that most of us are up against problems in terms of access to coverage for our patients? Is there a plan to go forward with any recommendations after today's panel discussion?

Dr Ichord: All of us who do this every day have strong beliefs about how children should be managed, and you've heard some suggestions about how to carry that into your own practices, and we do have an existing scientific statement that's a starting place for true practice guidelines.

Dr Roach: The closest guidelines that exist now are probably the American Heart Association guidelines that I talked about. That's not going to address every little issue, but it does get down into pretty intimate detail; there's a section in there, for example, about the extent to which you do a genetic workup on the family. Does it address everything? Probably not. It certainly addresses a lot of things for which we have marginal data where there is consensus one way or the other, and there are a few things even in this paper where as a group we just couldn't agree. In all probability the plan is every 4 or 5 years we'll have to meet again and review the evidence and evaluate how these have considerations changed or whether there is some aspect that we didn't cover the first time around. You mentioned rehabilitation. I think that is in there, but if there is something we left out, we could certainly put it in the next time.

Dr Hirtz: The other possibility is that the practice committee, in conjunction with the Academy of Neurology, publishes a practice parameter or practice guideline that is evidence-based. If we don't have the evidence to back up some of our statements or the level of evidence is weak, then it doesn't help much to publish this kind of a guideline except in the case where we feel that a practice is dangerous or unproven, and then it's good to get out the word that that is the case. I don't think that's the case here, but we certainly will give serious consideration to evaluating the evidence, and as soon as there is enough good evidence on any one of these topics, it would be appropriate to publish a practice parameter on it.

Dr Maria: One of the things that we've tried to do consistently over the last decade of this conference is to take this final session to reflect on what we think are among the many important questions, and the tour de force that Dr Yager pulled off in terms of summarizing what you all said today is to try to identify within those sets of key unanswered questions what rises to the top as a future research priority. What does each of you think is the most important first next question?

Dr Kirkham: The neonatal sinovenous thrombosis "should we treat or not?" would be probably at the top of my list, because we need good outcome data from that cohort. We need safety data, and then we need to do a trial. If we find out in the safety data that we don't need to do a trial because we don't have equipoise then that's fair enough, but the question would be whether we should anticoagulate neonates with sinovenous thrombosis.

Dr Roach: One of the problems we're up against is just how to get a toehold on doing a good, well-developed, scientific study. The one recurring theme over and over is "in the absence of data … ," and yet if you look at where we have managed to do studies, it's usually been in an area where we can cobble together a pure culture of something that is not just stroke. It's not one thing, so you can't just say stroke occurs fairly often and we're going to do a study on it, because you have to have not only that but a certain equivalence of age and causation in order to do a good study.

To some extent there are lots of areas where we need information. The next advance will come from the areas where we can come up with a pure culture of disease and sufficient numbers to do a good study on. Where are they? The highest incidence of stroke is in neonatal, so that is one place. Another would probably be a fairly predictable situation; for instance, a lot of kids have ischemic stroke with congenital heart disease, and a lot of them have the stroke when they're having catheter angiogram or in surgery, so even though these are not exactly predictable, at least the time when they're most likely to have a stroke is predictable. And that lends itself to a study. I don't know that these are the most important areas, but those are areas that could be studied and therefore would constitute lower hanging fruit.

Dr Ferriero: We should answer the question of whether we should cool newborns with ischemic stroke, and we should partner with our colleagues in neonatology to gain access to their data registry so that we can look at all these cool babies that we're collecting data on to see how many strokes there are and what the outcomes are in those kids.

Dr Ichord: Similar to others who have focused on the neonatal population because they're more of a captive audience, neonatal stroke is a model for epileptogenesis, and neonates represent a tremendous opportunity to evaluate predictors of later epilepsy, so answering questions about epilepsy is helpful: How aggressive should one be to identify and treat seizures? We tend to do it because we think it's the right thing to do, but we need more data on that, and the equivalent of that in childhood stroke is a smaller problem but still a very practical day-to-day management problem. How aggressive should we be at identifying and treating seizures in the setting of acute ischemic stroke? Second, what is the right antithrombotic treatment in acute ischemic stroke in a child, full-on anticoagulation or aspirin? This has been one of our targets for all the years we've been working on it, and it remains an urgent question.

Dr deVries: High on the list is a clinical trial for treating neonatal cerebral sinovenous thrombosis. There is another thing that I find very interesting: we have shown that very early on—within the first week—doing diffusion-weighted imaging in infants with neonatal arterial ischemic stroke reveals the high signal intensity in the descending cortical spinal tracts predicting hemiplegia, so very early on, even in the first week, you know which child is going to develop a hemiplegia. And we heard some very interesting data from Professor Taub about constraint-induced therapy, and I would be interested to get some evidence. When is it safe to start doing this? Can it be harmful doing it too early, or is there good reason to do it early?

Dr DeVeber: All of the above. For me still remains the very urgent question of aspirin versus anticoagulation. Since we can't use both, we have to pick one, so that would be the clinical trial we need to do.

Dr Vexler: I come from a different perspective because I am the only PhD on the panel. So I'm a big proponent of biomarkers because before knowing what is bad, what is so bad, we need to know how injury evolves, and one question, for example, that didn't come across in my session is the role of gender. Gender is very important in the reaction and the extent of protection or lack of protection in animal models.

Dr Yager: It's tough to be last when everybody has said everything, but I'd have to say that I'm a proponent for looking at biomarkers as well, and I think we should look at specific groups. A group like the cardiac group ought to be a group that is a captive audience. Generally, they have congenital heart disease. We generally know when they're going to undergo surgery, and they would be a good group to look at to determine their predisposing biomarkers. Another group is the migraineurs, and some of the work that Frank Sharp is doing is certainly intriguing in terms of figuring out if people with complicated migraines have a different genetic pattern than either people with strokes or simply people who have normal run-of-the-mill migraine headaches. So certainly I agree with everybody else's comment, and I don't think there's only one thing that we can look at. There are probably several.

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