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Pathogenesis, Neuroimaging and Management in Children With Cerebral Palsy Born Preterm

Alexander H. Hoon Jr^{1,*} and Andreia Vasconcellos Faria²

¹Johns Hopkins University School of Medicine, Phelps Center for Cerebral Palsy and Neurodevelopmental Medicine, Kennedy Krieger Institute, Baltimore, Maryland ²Johns Hopkins University School of Medicine, Radiology-Magnetic Resonance Research, Baltimore, Maryland

Abstract

With advances in obstetric and perinatal management, the incidence of intraventricular hemorrhage in premature infants has declined, while periventricular leukomalacia remains a significant concern. It is now known that brain injury in children born preterm also involves neuronal-axonal disease in supratentorial and infratentorial structures. The developing brain is especially vulnerable to white matter (WM) injury from 23 to 34 weeks gestation when blood vessels serving the periventricular WM are immature. Oligodendrocyte progenitors, which are beginning to form myelin during this time, are susceptible to attack from oxygen free radicals, glutamate, and inflammatory cytokines. Advances in imaging techniques such as diffusion tensor imaging provide a more complete picture of the location and extent of injury. Effective management of children born preterm with cerebral palsy is predicated on an understanding of sequential links from etiological antecedents to brain neuropathology as revealed with neuroimaging techniques to clinical phenotypes, toward focused interventions with measurable outcomes.

Keywords

apparent diffusion coefficient; diffusion tensor imaging; diffusion weighted imaging; fractional anisotropy; functional connectivity MRI; hypoxic-ischemic encephalopathy; intraventricular hemorrhage; large deformation diffeomorphic metric mapping; magnetic resonance imaging (conventional); magnetic resonance spectroscopy; neonatal intensive care unit; periventricular leukomalacia; small for gestational age; very low birth weight; white matter

INTRODUCTION

Cerebral palsy (CP) describes a group of nonprogressive motor-impairment syndromes which are secondary to a wide range of genetic and acquired disorders leading to brain dysgenesis or injury [Bax et al., 2005]. In addition to the motor manifestations, children with CP may have a wide range of associated impairments including epilepsy, feeding disorders,

orthopedic deformities, visual limitations, learning disorders, intellectual disability, and attention/behavioral dysfunction. Given the range and severity of clinical findings, medical/rehabilitative care is best conducted by a team, with expertise in the diverse problems and challenges these children face. While current long-term goals are to maximize mobility and educational, social, and vocational opportunities [Liptak, 2008], neuroprotective interventions in the neonatal period are being investigated that will diminish the cascade of apoptotic/necrotic cell death [Shah, 2010] as are cell-based therapies to restore brain function [Goldman et al., 2008; Pimentel-Coelho and Mendez-Otero, 2010].

When the diagnosis of CP is established, it is imperative to investigate etiology, which has implications for treatment, prognosis, and risk of recurrence. As 70–90% of children with CP have visible abnormalities on magnetic resonance imaging (MRI), it should be considered essential in the initial evaluation of children with significant motor delay, including those with CP. In children born preterm with CP, there are frequently associated risk factors [Hong and Paneth, 2008; Nelson, 2008; Schaefer, 2008] with brain injury often mediated through common final pathways involving hypoxia-ischemia and infection-inflammation [Keogh and Badawi, 2006].

The past two decades have witnessed a wide range of new obstetric and neonatal interventions, including referral of mothers for advanced obstetric monitoring, use of antenatal steroids and antenatal magnesium, sophisticated modes of ventilation, routine surfactant use, and total parental nutrition in high risk newborns. While postnatal steroid administration for the prevention of bronchopulmonary dysplasia has been associated with an increased risk of CP [Wilson-Costello et al., 2009], the overall result has been dramatically improved survival for neonates born preterm. However, there are persisting concerns about a wide range of later motor, cognitive, neuro-behavioral, and medical disorders in Neonatal Intensive Care Unit (NICU) graduates [Doyle and Anderson, 2010].

Approximately 40% of the 2–4/ 1,000 children with CP are born pre-term [Krageloh-Mann and Cans, 2009; Kirby et al., 2011]. Five to 10% of very low birth weight infants develop CP and 25–50% develop cognitive disorders including intellectual disability and learning disabilities. In children born preterm, CP is most closely linked with focal and diffuse white matter (WM)** injury broadly termed periventricular leukomalacia (PVL) [Rutherford et al., 2010]. However, as Volpe and colleagues have emphasized, PVL is often accompanied by neuronal/axonal disease in supratentorial and infratentorial structures [Volpe, 2009a].

Neuroimaging techniques are widely used in the NICU for diagnosis, management, and prognosis, and may be performed later in childhood for similar indications. In the NICU, imaging provides timely identification of central nervous system injury and recovery in preterm infants. Cranial ultra-sound detects hemorrhagic injury in WM [Grade 3–4 intraventricular hemorrhage (IVH)] and cystic PVL but may not detect diffuse WM injury, cerebellar pathology, or cortical dysgenesis at brain convexities [van Wezel-Meijler et al., 2010]. MRI techniques, including conventional MRI, magnetic resonance spectroscopy (MRS), diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI) are variably used to assess brain status and to permit the detection of more diffuse or subtle WM pathology as well as other supratentorial and infratentorial lesions. In children, certain MR

techniques, such as fcMRI (functional connectivity MRI) [Burton et al., 2009; Lubsen et al., 2011], are now being used to probe brain function and to complement other imaging modalities.

This review is intended to illustrate how the effective management of children born preterm with CP is predicated on an understanding of the sequential links, from etiological antecedents to brain pathophysiology with associated clinical phenotypes, to focused interventions with measurable outcomes. It is written from the perspective of the childhood evaluation of an infant born preterm who has or is at risk for CP.

EPIDEMIOLOGY

Although the Centers for Disease controls and Prevention has reported a decrease in the rate of preterm births in the last 2 years [Martin et al., 2010], the overall rate increased 30% between 1981 and 2005. This has led to increased research, both on the causes of premature birth [Ashton et al., 2009] and improved acute and long-term treatment [Marret et al., 2008].

Overall, prenatal factors are related to etiology in 70–80% of children with CP, with intrapartum asphyxia playing a role in 10–20% [Jacobsson and Hagberg, 2004]. A number of risk factors are linked to CP, including prematurity, low birth weight, multiple gestation, maternal thyroid abnormalities, intrauterine viral infection, male gender, hereditary thrombophilias, placental abnormalities, hypoxia-ischemia, and signs of intrauterine infection/inflammation. Epidemio-logic risk factors may act alone, in combination, or in the setting of other genetic or environmental factors to cause brain injury.

The maternal–fetal thyroid axis is of great importance in brain development, and any maternal history of thyroid problems should be strongly considered during later clinical assessment. Maternal thyroid dysfunction has been associated with pregnancy-induced hypertension, preterm birth, low birth weight, placental abruption, and fetal death. The fetal thyroid does not secrete hormone until 20 weeks gestation, and there is evidence that maternal thyroid hormone is important for fetal brain development early in gestation [de Escobar et al., 2008]. Iodine deficiency during pregnancy is associated with intellectual disability as well as spasticity and ataxia. While transient hypothyroxinemia is common in premature infants and has been associated with impaired neurodevelopmental outcomes [Hong and Paneth, 2008], it is not known whether maternal thyroid abnormalities significantly predispose premature infants to WM injury [Hagberg et al., 2005].

Intrauterine infection/inflammation and WM injury has generated a great deal of interest [Hagberg et al., 2005; Park et al., 2005]. The most common source is infection that ascends from the lower to the upper reproductive tract and infects the choriodecidual space and fetal membranes. Accumulating evidence supports the hypothesis that intrauterine infection can lead to elevated fetal blood and brain cytokine levels which, through a toxic effect on oligodendrocytes, result in cerebral WM injury and subsequent CP [Leviton et al., 2011]. A wide range of cytokines, chemokines, soluble receptors and growth factors in amniotic fluid, cord blood, and cerebrospinal fluid have been associated with the development of CP.

However, interpretation remains difficult as findings may be directly involved in brain injury, involved in repair or coincidental; in addition, levels may be related to a wide range of factors, including gestational age, perinatal and neonatal illness.

Inherited thrombophilias have been associated with placental dysfunction and CP [Gibson et al., 2005]. However, specific relationships between thrombophilia, placental dysfunction, and brain injury remain to be clarified.

Multiple gestations have an increased risk of CP when compared to singletons. This increased CP risk is primarily related to the higher incidence of preterm birth and to the higher risk of adverse neurological development of the survivor in the ante-natal death of one twin [Pharoah, 2006]. Children born after in vitro fertilization are at increased risk of CP, with risks primarily due to the high rate of multiple pregnancies, preterm birth, and low birth weight in this population.

Studies in children born preterm have shown that males have increased risk for neurodevelopmental disabilities including CP, despite similar perinatal, neonatal, and early childhood risk factors as females [Hintz et al., 2006]. Males born preterm have an increased risk for WM injury and IVH compared to females, which may be related to differences in intrinsic cell death pathways [Johnston and Hagberg, 2007]. This may have important implications for the ongoing development of neuroprotective interventions in the NICU.

Growth status at birth is an important factor to consider. A great deal has been written about long-term risks for small for gestational age (SGA) infants with lower cognitive scores, and increased learning and behavioral impairments [Lundgren and Tuvemo, 2008]. The risk for later neurodevelopmental impairment may be additive in the SGA infant born preterm [Pallotto and Kilbride, 2006]. CP is less common in this group.

PATHOPHYSIOLOGY

The understanding of the patho-physiology of CP in children born pre-term has been closely linked to neuroimaging. In the late 1970s and early 1980s, cranial ultrasound and computed tomography linked CP to brain hemorrhage and complications. In the later 1980s and early 1990s, the advent of MRI revealed that PVL was the major cause of injury. In the last decade, advanced MRI modalities have shown that PVL is often accompanied by diffuse, variable injury in cortical, subcortical, and cerebellar gray matter [Volpe, 2009a].

The increased risk of CP in the premature infants is related to complex interrelations between destructive and developmental mechanisms [Johnston and Hoon, 2006]. Volpe and colleagues have demonstrated that abnormalities in neurons and axons are the result of changes in the normal developmental trajectory of brain development, often initiated by hypoxic-ischemic or infectious-inflammatory cascades of injury. In addition to the WM vulnerability, associated neuronal injury in cerebral cortex, thalamus, and cerebellar relay nuclei may contribute to the explanation of the complex patterns of motor, learning/cognitive, and neurobehavioral problems encountered in affected children [Ligam et al., 2009].

Three main factors contribute to the increased risk of CP in children born preterm: immature blood vessels, a pressure passive circulation, and selective vulnerability of oligodendrocyte progenitors (which are susceptible to attack by oxygen free radicals, glutamate and inflammatory cytokines). Furthermore, it is now recognized that WM injury has both an extended time course as well as recurring sequentially over time [Glass et al., 2008].

An associated vulnerability in the preterm brain is injury to subplate neurons, which peak in number during the second half of gestation and later disappear through apoptotic cell death pathways [Folkerth et al., 2008]. These cells play an essential role in thalamic-cortical as well as intracortical connectivity [Kostovic and Judas, 2006]. Loss of precursor oligodendroglial cells and sub-plate neurons may be particularly important for determining outcome. Apoptosis propagated by secondary mediators may negatively influence survival of subplate neurons, important chaperones for connectivity. Far-reaching developmental deficits may, therefore, result from regions undersupplied by connecting WM that are important in coordination of different cortical functions.

Recent attention has been given to ischemic or hemorrhagic cerebellar injury or underdevelopment [Volpe, 2009b]. The cerebellum develops rapidly from 24 weeks to term, with a fivefold increase in volume and a 30-fold increase in surface area during this time. There is a wide range of potential clinical correlates of cerebellar abnormalities including motor disturbances, cognitive impairments, attentional deficits, and social-affective disturbances.

NEUROIMAGING

Imaging Modalities and Indications in the NICU

For a variety of well-accepted reasons, cranial ultrasound is widely used in the NICU [Ment et al., 2002]. It is inexpensive, safe, and repeatable. Cranial ultrasound provides visualization of the evolution of injury and can be used in the discussion of outcome with parents and families.

In addition to the well-recognized findings of ventriculomegaly in IVH and PVL, the presence of isolated ventriculomegaly should be considered when evaluating a neonate (or when later assessing a child). It is often a proxy for loss of cortical WM or gray matter and as such a measure to establish prognosis [Ment et al., 1999]. Ventriculomegaly may also be a sign of underlying genetic disorder [Toi et al., 2009].

In the extremely preterm infant, the cerebellum is a recognized site of hemorrhage or underdevelopment, which is detected using cranial ultrasound through a posterior fontanelle (although the views may be limited) [Ecury-Goossen et al., 2010]. Findings may be unilateral or bilateral. Although the full ramifications of cerebellar pathology are currently not known, recent information indicates that the cerebellum has an important role in learning new information as well as coordination of motor activity [Volpe, 2009b].

DWI has improved the early identification of ischemic brain injury in high risk premature and term infants, prior to visualization on conventional MRI [Ramenghi et al., 2009]. It is being used to identify infants for neuro-protective interventions [Chau et al., 2009a]. MRS is

another advanced technique that provides measures of brain biochemistry by measuring metabolite concentrations in vivo. Various molecules including neuronal and glial markers, neurotransmitters, energy metabolites, membrane and myelin markers can be measured. Proton MRS (^1H -MRS) has been used in the term infant with acute perinatal asphyxia.

Imaging in Childhood

As chromosomal microarray has improved the detection of subtle genetic abnormalities not visible with a standard karyotype [Miller et al., 2010], MRI and newer advanced techniques extended the understanding of the spectrum of brain malformations by identifying milder abnormalities than were visible with earlier techniques [Chau et al., 2009b; Rutherford et al., 2010]. MRI is sensitive in detecting PVL, other perinatally acquired lesions, and subtle congenital anomalies of brain development: it detects abnormality in 70–90% of affected children [Ashwal et al., 2004].

In childhood, PVL is often seen on MRI as WM loss and gliosis, enlarged, scalloped ventricles and thinning of the corpus callosum (Fig. 1). The degree of WM loss, as reflected in progressive ventriculomegaly, correlates with the severity of motor and cognitive impairment [Melhem et al., 2000].

The thalamus has numerous connections with many other structures including the cerebral cortex. Quantitative and DTI measurements have shown both volume loss and microstructural abnormalities in the thalamus, likely reflecting both neuronal loss and axonal injury [Nagasunder et al., 2011]. Thalamic injury commonly occurs in association with PVL [Pierson et al., 2007]. The patterns of thalamic injury in the preterm infant differ from those seen in acute perinatal hypoxic ischemic encephalopathy in full-term neonates [Hoon, 2005], as seen in Figure 2. Children with thalamic injury often have dyskinesias as an integral part of their clinical phenotype.

Signal and volumetric abnormalities have been shown to correlate with the type and severity of neurologic sequelae [Arzoumanian et al., 2003]. WM abnormalities correlate with long-term motor outcome [Nanba et al., 2007; Woodward et al., 2006]. Compared with other assessment methods and neurological tests, MRI has the greatest accuracy in predicting combined motor outcomes, with 90% specificity; however, the sensitivity is low [Spittle et al., 2009]. This lack of sensitivity is attributable, in part, to the relatively high water content of the immature, unmyelinated WM, resulting in a long T_1 and T_2 relaxation, similar to that associated with injury. Moreover, the lack of contrast within the WM in conventional MRI hinders more specific correlations between prognosis/ function and injury to specific brain regions.

Conventional MRI, which has proved sensitive for the identification of PVL, is not able to accurately determine the extent and nature of injury in specific WM tracts. Advanced imaging techniques such as DTI now provide a more complete picture of the patterns in PVL. DTI, which uses directionality of water diffusion to identify central WM tracks, improves visualization of both brain maldevelopment and injury. This technique measures the water diffusion in the brain that, particularly in WM, is anisotropic (follow the orientation of bundles of axons and/or their myelin sheaths). Consequently, this method

provides information about WM anatomy, making it possible to map tracts and individualize WM subunits.

It has been shown that DTI indices, such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC), reveal information not apparent on conventional MRI in the first year of life [Neil et al., 1998] and are more sensitive to disruption in WM than any other imaging method [Neil et al., 2002; Lee et al., 2005; Son et al., 2007]. Particularly in children with CP, DTI can add anatomic specificity and quantitative information to the evaluation of the WM microstructure. DTI has been widely used to determine patterns of WM injury [Nagae et al., 2007; Son et al., 2009]. Recent reports suggest that it may be of benefit in measuring changes in neural plasticity associated with rehabilitative interventions [Trivedi et al., 2008].

The degeneration of various motor and sensory pathways, as well as deep gray matter structures, appears to be important in determining the patho-physiological mechanisms in children with congenital WM injuries [Thomas et al., 2005]. Huppi found a 20% decrease in DTI relative anisotropy of the sensorimotor tracts in the posterior limb of the internal capsule in preterm infants who had WM injury on MRI [Huppi and Dubois, 2006]. Similarly, differences on DTI were detected in the posterior regions of the corpus callosum, internal capsule, and corona radiata in children with CP [Hoon and Melhem, 2000].

While these studies, for the most part, focused on the correlation between DTI in the pyramidal motor tract and motor function [Son et al., 2009], thalamo-cortical projections to or from the sensory cortex play an important role in the pathophysiology of motor disability in children with WM injury. In a preliminary study using DTI, we showed that thalamic-cortical projections to or from the sensory cortex, rather than classical pyramidal motor tracts, played an important role in the pathophysiology of motor disability in children with PVL [Hoon et al., 2002]. These posterior thalamo-cortical somatosensory connections are somato-topically organized and project broadly to association and visual cortex. Injury in these pathways may impair peripheral sensory input to the cortex and reciprocal corticothalamic projections. Posterior thalamic radiation, which connects the pulvinar and the lateral geniculate nucleus to posterior cortical regions, appeared especially disrupted. Retrograde injury to these tracts could explain the damage to posterior thalamic nuclei.

In a follow-up study of 24 children with PVL, we reported that both the retrolenticular part of the internal capsule and the posterior thalamic radiation—major constituents of the thalamocortical/corticothalamic pathways—were the WM tracts with the most frequent and severe injuries, replicating our previous report [Nagae et al., 2007]. Most recently, we have linked thalamo-cortical injury to sensory motor function in the same population of children [Hoon et al., 2009].

These studies raise the hope that future treatment interventions might use strategies to more specifically target injured pathways. Traditional interventions have focused on motor control and strength. The challenge is to develop treatment directed toward injured central sensory (thalamocortical) as well as motor pathways to maximize functional potential.

DTI-LDDMM Research

Methodology—Although these neuroimaging studies described above delineated the general anatomic basis of the functional impairment in children with CP, they were only able to delineate components of the affected pathways that could be manually outlined in 2D, based on anatomic landmarks. On the other hand, when based on 3D tractography, the studies face scrutiny about observer influence and technical limitations. In addition, these methods are evaluator dependent with regard to the chosen definition of the regions of interest. Therefore, it has been suggested that these previous studies are insufficient to fully describe the neuroanatomic changes, due to both lack of coverage and lack of precision.

A global and integrative analysis of neuroanatomy is essential for understanding the pathophysiology of CP. It is likely that the functional disabilities can be better explained by the interaction among multiple abnormal areas, both WM and neuronal, than by the effect of one or more isolated regions. Second, as mentioned previously, CP describes a heterogeneous group in terms of etiology, type of lesions, functional status, and outcomes. An integrative and objective analysis of different parameters in different regions could help in determining what, if any, are the neuroanatomic similarities between different subgroups of children with CP, and how different insults to the developing brain contribute to differences in motor and cognitive ability. The identification of similar patterns of injury may improve treatment as well as refine our ability to determine a neurodevelopmental prognosis.

This global and integrative study was previously unfeasible, partly because of the lack of a method that allowed objective and evaluator-independent analysis of anatomical structures of the whole brain, especially WM. This is attributable to two factors: (1) lack of anatomic contrast to reveal intra-WM structures by conventional MRI and (2) lack of a comprehensive and quantitative evaluation system to assess anatomic status.

DTI solved the first issue by providing high contrast imaging within WM. The solution for the second issue could be based on automated brain segmentation, a process intrinsically dependent on methods for brain normalization and for codification of the location information. State-of-the-art normalization techniques provide highly accurate registration (meaning morphing the subject brain into a standard atlas or template). This allows us to transpose a given standardized parcellation of anatomical structures (location information), with biological meaning, defined in the template to each individual brain for comparison.

One of these highly accurate normalization techniques is large deformation diffeomorphic metric mapping (LDDMM). While the core algorithm of LDDMM was proposed in 1997 by Miller and Wang [Wang et al., 2007], it has only recently been recognized that LDDMM is optimally tailored for brain anatomy. LDDMM has several important features: it is highly nonlinear and thereby has the ability to match the shapes of two brains; it incorporates multiple image contrasts, including DTI, and it performs deformation that simultaneously satisfies all contrasts [Ceritoglu et al., 2009]. It is a reversible transformation, meaning a subject image can be transformed to template as well as the template to the subject image within the same transformation framework.

The standard brain atlas used is “JHU-DTI-MNI” atlas [Mori et al., 2008], which is a single-subject template in the International Consortium for Brain Mapping space and is extensively segmented and labeled to around 200 regions [Oishi et al., 2008]. When the registration by LDDMM of each individual to the template (Atlas) is completed, the parcellation defined in the Atlas space can be inversely transposed to define these 200 brain regions automatically in each patient, thereby enabling us to measure the volumes, shapes, and various MR-based parameters, such as T₂ signal, ADC, and FA. In terms of granularity, this is much less than voxel-based analysis and works as a conversion from pixel-based to anatomy-based analysis. This procedure can also be considered as a special type of spatial smoothing filter, with the atlas providing structure-specific filters. The LDDMM-based automated segmentation has been shown to be fairly accurate (Dice index between automated and manual definitions of 0.75 and higher), for young [Faria et al., 2010], aged, Alzheimer [Oishi et al., 2009], and CP populations [Faria et al., 2011], which rivals test–retest manual segmentation accuracy (typically 0.8–0.9).

The Atlas-based approach effectively reduces the vast 3D spatial information (that initially corresponded to more than one million points, where each point is one image voxel) into a manageable size. Each patient is characterized by a matrix where the rows correspond to the 100–200 regions in which they are parceled and each column corresponds to the features associated with them (such as volume, FA, and ADC). These matrices can be used to group comparisons, to find anatomic correlation with clinical performance, to determine subgroups in terms of anatomical and/or functional characteristics and, potentially, to find function and/or prognosis predictors. They can also be represented graphically as a quantitative map of anatomical features.

For example, Figure 3 shows the results of the quantitative Atlas-based analyses applied to children with CP and enriched by data from typically developing volunteers. It is easy to determine, by visual analysis, that for instance, the superior longitudinal fasciculus (SLF) is abnormal in the two children with CP. However, it is not straightforward to determine whether they are beyond the normal range of variability. This characterization is possible only by quantifying each segment, in each subject, using the Atlas approach. For diseases like CP, which is known as a highly inhomogeneous entity, this type of evaluation provides a highly individualized view of brain anatomic status.

Currently, advanced techniques such as LDDMM analysis and fcMRI are beginning to be applied in a wide range of disorders including CP. In the future, the combination of DTI and fcMRI [Burton et al., 2009; Lubsen et al., 2011], and imaging methods to be developed, offers the potential to not only understand the relationship between structure and function but also to evaluate the effects of various interventions. This will be of great benefit as, at present, it is often difficult to predict who will respond to which intervention.

CLASSIFICATION

There has been recent recognition of the need to accurately classify children with CP and reliably measure the effects of intervention. A number of groups have formed to address this area, including the Task Force on Childhood Motor Disorders [Sanger et al., 2003, 2006],

National Institute of Child Health and Human Development, Neonatal Research Network [Wilson-Costello et al., 2009], and the European Cerebral Palsy Database [Christine et al., 2007]. Research from these groups has been of great benefit in standardizing terminology and classification and providing a common language for communication.

CLINICAL PHENOTYPES

CP is often classified into specific phenotypes (subtypes) according to neurological findings and the body limbs that are predominately affected (Fig. 4). A recognized classification system divides the phenotypes into bilateral and unilateral involvement [Krageloh-Mann and Cans, 2009]. This distinction is useful both in evaluating etiology and directing management.

Cerebral Palsy Phenotypes

Spastic CP is the most common form of CP and is closely associated with prematurity [Krageloh-Mann and Cans, 2009]. It is further categorized according to the distribution of limbs involved. In spastic diplegia, the legs are more affected than the arms. In spastic quadriplegia, all four limbs and usually the trunk and muscles that control the mouth, tongue, and pharynx are affected. Individuals with spastic quadriplegia often have intellectual disability, seizures, sensory impairments, and other medical problems. In spastic hemiplegia, arm function is usually more affected than lower extremity function and is commonly associated with asymmetric IVH in children born preterm [de Vries et al., 1998; Roelants-van Rijn et al., 2001].

Dyskinetic CP is characterized by fluctuating abnormalities in muscle tone and movement. The term choreoathetoid CP characterizes a form of dyskinetic CP commonly associated with kernicterus. Dystonic CP may be associated with basal ganglia injury in pre-term children as well as with hypoxicischemic encephalopathy (HIE) in the term infant.

Ataxic CP is characterized by abnormalities of voluntary movement involving balance and position of the trunk and limbs in space. Ataxic CP may be associated with cerebellar injury in children born preterm. The term mixed CP is used when more than one type of motor pattern is present and when one pattern does not clearly predominate over another.

PRINCIPLES OF CLINICAL MANAGEMENT

Neuroplasticity and Selective Vulnerability

A key starting point in the discussion of management is based on an understanding of neuroplasticity [Johnston, 2009] and patterns of selective vulnerability. The human brain grows rapidly from conception through early childhood. During childhood, approximately half of brain synapses are kept due to stimulation through activity and half are eliminated. Neuroplasticity is based on this selective synaptic pruning, and is characterized by the ability of the brain to adapt to environmental changes, to store information in memory associated with learning and to recover from brain and spinal cord injury.

A key concept in understanding both the neurobiology and management of CP is selective vulnerability [Johnston, 1998]. Selective vulnerability refers to the susceptibility of specific regions and cells to insults during specific times in brain development. It is closely linked to an understanding of etiologic causes of CP, including PVL, perinatal HIE, kernicterus, and genetic–metabolic disorders. Between 24 and 34 weeks of gestation, immature oligodendroglia are especially susceptible to injury, while in HIE in full-term infants and kernicterus, the primary vulnerability is in deep gray structures.

It is now known that there are endogenous reparative mechanisms to counteract the brain injury types found in children [Haynes et al., 2011]. Neurogenesis and corticogenesis are now known to occur even in the adult brain after ischemic injury, and although many of the cells produced will ultimately die, they may have important functions of guiding and re-establishing connections. Connectivity continues to be modified in the post injury period and for many years in the premature infant. Neurotrophic factors are essential to this process.

In CP, as well as in other childhood neurodevelopmental disabilities, the two overarching questions in regard to neuro-plasticity and rehabilitation involve: (1) the nature of the relationship between amount/timing of intervention and outcome and (2) the development of reliable and valid outcome assessments to measure the effectiveness of specific medical and rehabilitative interventions.

Specifics of Management

Comprehensive management of children with CP includes both accurate diagnosis and effective treatment strategies. Management is based on recognition that each child requires a unique combination of medical and rehabilitative interventions, developed through a team approach and tailored to family structure and goals. Specialists in orthopedics, neurosurgery, genetics, ophthalmology, gastroenterology, neurology, physical medicine and rehabilitation, psychiatry and neurodevelopmental pediatrics may be integral in developing a comprehensive plan. Physical and occupational therapists, speech-language pathologists, audiologists, clinical and behavioral psychologists, special education consultants, and social workers also provide important input.

Management may be divided into rehabilitative, medical, and surgical components. Rehabilitative interventions include conventional therapeutic approaches, serial casting, orthotic bracing, strength training, aquatherapy, hypnotherapy and technology systems such as augmentative communication and power mobility. The focus in physiotherapy has shifted from traditional physical and occupational therapy to approaches combining principles of motor learning, strength and fitness training. Specialists in social work and psychology, aware of the effects of motor disability on other aspects of childhood development, may be of great benefit in fostering social–emotional growth and family coping/adaptation.

Commonly used oral medications include baclofen, diazepam, levodopa, and trihexyphenidyl, as well as therapeutic botulinum toxin [Deon and Gaebler-Spira, 2010]. Recently, there have been reports of possible detrimental long-term consequences of botulinum toxin injection which must now be considered prior to intramuscular injection [Steinbok, 2006]. Tetrabenazine has been more recently used successfully in selected

patients with dyskinetic forms of CP [Vidailhet et al., 2009]. Surgical interventions include orthopedic tenotomies, tendon transfers, and osteotomies.

Neurosurgical procedures include intrathecal baclofen (ITB), selective dorsal rhizotomy (SDR) [Russman, 2008] and, in very specific clinical situations, deep brain stimulation [Brennan and Whittle, 2008]. ITB and SDR are used in many centers for children with spastic diplegia. Both are costly procedures and require surgeons with expertise. When patients are carefully selected and followed in a specialized program, there may be benefits in both ease of care as well as improved functional outcomes. An important difference is that an ITB pump may be removed, while SDR is permanent. However, ITB requires close ongoing management, while SDR is a single procedure. With both procedures, outcome is optimized when combined with rigorous, ongoing therapy.

ITB is an excellent therapeutic approach for children with refractory spasticity (or dystonia) [Brochard et al., 2009]. The pump delivers microgram amounts of baclofen into the intrathecal space via an implanted, programmable system. ITB provides titratable reductions in spasticity using doses of baclofen in micrograms, rather than milli-gram dosing for oral doses, and with a lack of the adverse effects often associated with higher doses of oral baclofen. The pumps that are generally used can be programmed to provide a continuous infusion rate or intermittent bolus dosing [Senaran et al., 2007].

Prior to pump placement, a 50 lg bolus of baclofen is frequently given by lumbar puncture, with a 6–8 hr period of close observation for reductions in spasticity by both a therapist and family member. At the time of pump insertion, intrathecal catheter placement site is important, with higher placement associated with greater benefit to the upper extremities.

ITB often improves ease of care and comfort. While there are reports of functional improvements in children with spastic diplegia using ITB, replication of findings in prospective, randomized trials has not been done to date [Kolaski and Logan, 2007]. Although there have been concerns of worsening scoliosis with ITB, a recent report indicated that ITB did not affect curve progression, pelvic obliquity, or the incidence of scoliosis when compared to a similar group of control children [Steinbok, 2007].

Effective ITB management requires a team approach and a committed family. Risks, treatment goals, and parental expectations of benefit should be completely outlined prior to surgery. After pump placement, ongoing surveillance is necessary for potentially serious side effects, including severe acute withdrawal secondary to catheter dysfunction, increased hypertonicity associated with catheter kinking or dislodgement, signs of infection, and central nervous system depression or loss of function from excessive dosing [Nordmark et al., 2008].

SDR is a surgical procedure in which 30–50% of sensory nerve rootlets are selectively cut to reduce lower extremity spasticity and improve function [Langerak et al., 2008]. The optimal group of patients is 4–10-year-old children born preterm who have relatively pure spastic diplegia, minimal or no extrapyramidal signs, and good antigravity strength/selective motor control. Some surgeons use intraoperative nerve stimulation to determine which rootlets to cut, while others feel this is not required.

While there are reported long-term functional benefits with SDR [Steinbok et al., 2005; Cheong et al., 2008], long-term concerns must be considered, including hip subluxation, spinal stenosis, and pain [Horridge et al., 2011; Maunu et al., 2011]. As with ITB, a team approach, regular ongoing therapy, active family involvement, and education are critical.

THE ART AND SCIENCE OF CLINICAL DECISION MAKING

History

For the clinician evaluating a child born prematurely with suspected or confirmed CP, a complete history is the starting point. Key factors to consider include evidence of maternal prenatal risk factors (e.g., thyroid disease, substance abuse, infection, diabetes), prenatal course, appropriate for gestational age/SGA status, and NICU Course including ventilation, systemic infections, peak bilirubin, ultrasound imaging, and results of visual and hearing evaluations. It is always important to take a detailed family history looking for evidence of genetic disorders or environmental teratogens, which may affect both treatment and prognosis.

Examination

The adage “When all else fails, examine the patient- for more is missed by not looking than by not knowing” should always be remembered. Growth, especially in head circumference, should be carefully measured. Poor postnatal head growth is strongly associated with an increased risk for CP [Holsbeeke et al., 2009]. Clinical evidence of a hearing disorder, visual impairment, and/or possible underlying genetic disorder should always be considered.

On neurological examination, children with the diagnosis of spastic diplegia may have primarily spasticity in the lower extremities, truncal hypotonia, and upper extremity dyskinesias. When medical management is being considered, the target neurological finding should be carefully identified.

Neuroimaging

Direct review of the neuroimaging from the nursery period as well as during childhood should be done whenever possible to detect important abnormalities that may have been missed [Horridge et al., 2011]. The extent of ventriculomegaly clinically correlates with degree of impairment and with prognosis [Maunu et al., 2011]. For example, those with more severe involvement are likely to develop quadriparesis and potentially benefit from ITB, if other medical options are insufficient. For those children with basal ganglia/thalamic injury who have significant dyskinesias, especially dystonia, levodopa may be a good medication to improve function.

Other Testing

In some children born preterm with “cerebral palsy,” history, examination, or imaging may suggest other etiologies, especially neurogenetic disorders. If there is any suspicion in this regard, input from an experienced neurogeneticist is critical, for specific diagnoses may have very different prognoses and recurrence risks.

Treatment Plan

It is very important that clinicians and families agree on specific treatment as well as overall management. Recognized goals include improvements in function, communication, and ease of care; decreased pain and discomfort; and recognition of a need for orthopedic surgery. Successful treatment is closely linked to appropriate patient selection. Including children with CP in the decision-making process whenever feasible is critical to implementation and success. Finally, treatment should be integrated into the lifestyles and other activities/commitments of individual families.

Furthermore, the goal of treatment (e.g., improved function, improved ease of care and/or decreased pain) should be completely discussed with the child and family [Holsbeeke et al., 2009]. Other practical considerations in optimizing management include: (1) the recognition that a specific medical treatment or therapy may be embraced by one family but rejected by another (even when the overall clinical findings are similar) and (2) the need for effective care coordination. The latter has led to the development of the medical home model. It should be noted that care coordination may also be provided through insurance companies and state programs.

In summary, clinicians who evaluate and treat children with suspected or diagnosed CP need to be informed of the multifactorial causes of CP in children born preterm and the variable patterns of injury. This synthesis will lead to improved care management, including early diagnosis, better prognostication, and the selection of effective treatment strategies. Finally, this integrated understanding promotes family knowledge, coping, and adaptation.

CONCLUSIONS

1. Brain injury in children born pre-term is often diffuse and variable in location and extent.
2. Effective management of children born preterm with CP is predicated on an understanding of the sequential links from etiology, to brain neuropathology and clinical phenotypes, to focused interventions with measureable outcomes.
3. The combination of new research imaging techniques combining structure (DTI-LDDMM) and function (fcMRI) offers great promise to advance understanding of CP pathogenesis and improve treatment. These tools have the potential to accurately and automatically describe the neuro-pathology of brain injury in children with CP by providing both detailed anatomical as well as functional information. The resulting structure–function relationships could potentially be used to both design targeted intervention studies as well as to measure treatment effects.

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“Three main factors contribute to the increased risk of CP in children born preterm: immature blood vessels, a pressure passive circulation and selective vulnerability of oligodendrocyte progenitors (which are susceptible to attack by oxygen free radicals, glutamate and inflammatory cytokines)”

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“An integrative and objective analysis of different parameters in different regions could help in determining what, if any, are the neuroanatomic similarities between different subgroups of children with cerebral palsy, and how different insults to the developing brain contribute to differences in motor and cognitive ability”

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“Selective vulnerability refers to the susceptibility of specific regions and cells to insults during specific times in brain development. It is closely linked to an understanding of etiologic causes of cerebral palsy”

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Fig. 1. The two axial T₂-weighted images show the ventricular scalloping (white arrows) and loss of WM posteriorly (black arrows) in two children with spastic diplegia. Gliosis is often better seen on fluid attenuated inversion recovery images.

Fig. 2.

The four panel set of axial fluid attenuated inversion recovery images shows the anatomical differences in thalamic injury (white arrows) in two children with term acute HIE (A and B) and in two children born preterm (C and D). Note the periventricular WM gliosis (black arrows) indicative of PVL in C and D.

Fig. 3.

Demonstration of automated abnormality detection using the atlas enriched by a normal database of developing brains. The ADC and FA maps of one control and two CP patients show the large ventricles and WM atrophy, particularly in Patient #1, and the abnormal contrast in the deep WM, secondary to PVL, particularly in Patient #2. The FA and volume z-score maps (second and third lines) show the degree of deviation from control values. These maps are shown in the atlas space, with which abnormal WM tracts can be identified at a glance. Linear regressions of FA and the volume (mm^3) of the left SLF (arrows and surrounded area) of normal subjects (green dots) are shown by the continuous lines. Shaded area is 95% confidence interval of the curve and dashed lines are the prediction interval for z-scores of ± 2 (gray and red lines, respectively), -3 (blue line), and -4 (yellow line). Yellow squares are the results from CP patients. The color surrounding the images and circle colors in the scatter plots identify the subjects. Reprinted with permission from Faria AV, Hoon A, Stashinko E, Li X, Jiang H, Mashayekh A, Akhter K, Hsu J, Oishi K, Zhang J, Miller MI, van Zijl PC, Mori S, *Neuroimage*, 2011, 54, 1854–1861; Erratum in: 2011, *Neuroimage*, 55, 1912–1913, © Elsevier. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

BILATERAL			UNILATERAL
Spastic	Extrapyramidal		Spastic hemiplegia
Spastic diplegia	Dyskinetic	Ataxic	
	Dystonia	Hypotonic	
Spastic quadriplegia (Tetraplegia)	Chorea (Choreoathetosis)	Spastic	
	Athetosis		
	Hemiballismus		

Fig. 4.

CP can be subdivided into bilateral (both sides affected) and unilateral (one side affected) forms. Some clinicians use the term “Extrapyramidal” for all who do not have spasticity, while others subdivide affected children into Dyskinetic (dystonia, chorea, choreoathetosis, athetosis, and hemiballismus) and Ataxia groups. Certain types of CP (dyskinetic, ataxic, mixed, and spastic quadriplegia) involve the entire musculoskeletal system; other forms of spastic CP (diplegia, hemiplegia) are localized to particular regions of the body.