STRATEGIES FOR THE EARLY DIAGNOSIS OF CEREBRAL PALSY

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Strategies for the early detection and diagnosis of cerebral palsy include multiple measures of the underlying brain abnormalities and their neurodevelopmental consequences. These measures can be grouped into the categories of pathogenesis, impairment, and functional limitation. Neuroimaging techniques are the most predictive measures of pathogenesis of cerebral palsy in both the preterm and term infant. Measures of neurological impairment focusing on muscle tone, reflexes, and other features of the neurological examination are poorly predictive in the first months of life. Detection of functional limitations manifested by motor developmental delay is sensitive and specific for later cerebral palsy, but not until well into the second 6 months of life. Abnormal spontaneous general movements in the infant 16 to 20 weeks postterm and earlier reflect functional limitations in the first months of life and have been shown to predict later cerebral palsy. Recognition of abnormal spontaneous general movements may improve early detection and diagnosis of cerebral palsy if these techniques can be successfully incorporated into organized follow-up programs and developmental surveillance. (J Pediatr 2004;145:S8-S11)

Cerebral palsy (CP) is a group of disorders of movement and postural control caused by a nonprogressive defect or lesion of the developing brain. CP is in part a developmental diagnosis, a description of motor symptoms that, taken together, are disabling. An etiologic diagnosis may be known, but it is not required, nor is information about underlying brain pathology. The diagnosis itself does not imply a specific prognosis. Efforts to diagnose CP that focus on specific causes do not address the motor symptoms central to CP and are unlikely to be sufficiently sensitive or specific in their utility.

The purposes for diagnosis, especially early diagnosis, are many. Different purposes may require different approaches to identification and different levels of timing, sensitivity, and specificity. For example, diagnosis for prevalence determination should be sensitive but may not need to be early. In contrast, diagnosis to determine eligibility for effective early interventions must be made early and should be sensitive, but need not be highly specific, because the intent is to avoid errors of exclusion. Diagnosis for inclusion in clinical trials or for tailored treatments may need to be very specific based on the requirements of the trial or the nature of the treatment. Diagnosis for long-term prognosis and secondary or tertiary prevention should be sensitive and specific but need not be early. Indeed, the specificity of the diagnosis will improve as the child ages and the nature of the disability evolves. Diagnosis or, better stated, detection of CP should be distinguished from the detailed diagnostic characterization of the functional, medical, and social components of a complex neurodevelopmental disability such as CP. The understanding of the profile of a child’s disability across multiple domains is an ongoing process necessary for appropriate treatment and future planning. Early diagnosis, or detection, of CP is more straightforward conceptually but complicated in its implementation.

Approaches to early diagnosis of CP can be grouped according to categories in the outcomes model of the National Advisory Board of Medical Rehabilitation Research, which defines categories of pathogenesis, impairment, functional limitation, disability, and societal limitation.

PATHOGENESIS

Although it is attractive to attempt early diagnosis of CP by identifying factors closely related to the pathogenesis of CP, the sensitivity and specificity of such risk factors have been disappointing. For example, some single risk factors such as low, very late Apgar values.
scores with high predictive value occur so rarely as to be useless outside exceptional cases. More common early factors associated with subsequent CP such as neonatal seizures are less predictive and therefore less useful in the individual case. Combinations of risk factors improve the situation, but in the landmark report from the National Collaborative Perinatal Project, combining (or compiling) the most sensitive risk factors extending from preconception to the neonatal period yielded a sensitivity of only 36.7% with a positive predictive value of 2.8%. That is, 63.3% of infants with CP will not have a profile of high risk, and 97.2% of those with the high-risk profile will not have CP. These are data based on pregnancies in the late 1950s through mid-1960s and do not directly address factors now known to be associated with CP such as maternal or fetal thrombophilia and some aspects of maternal infection or chorioamnionitis, and they predate assisted reproductive technologies that, by increasing multiple gestations and thereby low birth weight, increase risk for CP.

Even an updated risk factor approach is unlikely by itself to be sufficiently sensitive or specific to be useful in the early diagnosis of CP for any purpose. However, risk remains critical in understanding complex pathogenetic pathways leading to CP, including the potentially complex interaction of infectious, genetic, other biologic, demographic, and socioeconomic factors. Improved understanding of these relationships is important for the prevention of CP.

Brain neuroimaging offers a more direct indicator of the pathogenesis of CP. Brain ultrasound and MRI usually detect the abnormalities associated with subsequent diagnosis of CP. Data supporting use of neuroimaging are best shown in the clinical scenarios of the premature infant with very low birth weight and the term neonate with clinical encephalopathy.

The neuroimaging findings of interest in infants with very low birth weight are intraventricular hemorrhage, white matter cystic lesions, and ventriculomegaly as primary results of hemorrhage, hypoxia or ischemia. Cranial ultrasound is the most extensively studied neuroimaging modality in the preterm infant and demonstrates high correlation with the neuropathologic findings of hemorrhage and cystic periventricular leukomalacia (PVL). Although ultrasound examination in the first week of life is important in determining acute treatment of the preterm neonate, examination at term age is more sensitive for prognostic purposes, especially in identifying cystic PVL and ventriculomegaly associated with the subsequent development of CP. In a study of 777 survivors with low birth weight, cystic PVL or ventricular enlargement was strongly associated with CP at 2 years, yielding an odds ratio of 15.4 (7.6-31), sensitivity of 54%, specificity of 95.8%, and positive predictive value of 52%. Sensitivity was improved (61%) by using any degree of germinal matrix or intraventricular hemorrhage as the indicator, but with the expected decrease in specificity (84%) and positive predictive value (25%). Currently, infants with very low birth weight should receive ultrasound examination at term to detect grade 3 or 4 intraventricular hemorrhage, cystic PVL, and ventricular enlargement, which are associated with poor neurodevelopmental outcome, including CP.

Studies of imaging in term infants have necessarily focused on those with encephalopathic indications for neuroimaging. These studies are much smaller than those in infants with very low birth weight because of fewer available subjects. Nevertheless, abnormalities of the basal ganglia and thalamus on MRI in the first 2 to 8 days of life are strongly associated with adverse outcomes, including CP. Signal abnormalities in the posterior limb of the internal capsule are independent contributors to subsequent CP and are a marker for basal ganglia and thalamic injury. Absence of normal signal in the posterior limb of the internal capsule in term infants with encephalopathy predicted abnormal neurodevelopmental outcome at 1 year with a sensitivity of 90%, a specificity of 100%, and a positive predictive value of 100%.

Magnetic resonance spectroscopy and diffusion weighted imaging may offer additional prognostic information. Current recommendations in term infants with encephalopathy are to perform magnetic resonance imaging in the first 2 to 8 days of life and, if available, supplement with diffusion weighted imaging and magnetic resonance spectroscopy. It should be remembered that the majority of CP diagnosed in term infants in developed countries is caused by prenatal influences and is not associated with significant neonatal encephalopathy.

Such an asymptomatic infant would therefore not be selected for neuroimaging as a neonate. However, as the infant developed and abnormal neuromotor signs and symptoms became apparent, neuroimaging would be a key part of the diagnostic assessment of the pathogenesis and severity of the associated brain injury.

**IMPAIRMENT**

Impairment—defects at the organ or system level—includes abnormalities in muscle tone, strength, and control; involuntary movements; and other findings on the neuromotor examination such as motor asymmetries, abnormal primitive reflexes, and late development of postural responses. Although diagnosis of CP based on impairment is traditional, its use in early diagnosis has been frustrating.

The most striking demonstration of the difficulty of basing the early diagnosis of CP on the infant neurologic examination is found in the classic articles from the National Collaborative Perinatal Project. In this large prospective multicenter study, infants were followed from pregnancy to age 7 years, and neurologic status in infants was compared with the presence or absence of CP at 7 years. Only 23% of children with CP at 7 years had an abnormal neurologic examination as a newborn. Although an additional 34% with CP at age 7 had a suspect newborn examination, fully 43% of 7-year-old children with CP had a normal newborn neurologic examination. Prediction at 4 months of age was only marginally better. Thirty-three percent of children diagnosed with CP at age 7 years had an abnormal neurologic examination, 31% were suspect, and 36% were judged normal neurologically. Problems with false positives were equally remarkable. About half of children diagnosed with CP at 1 year of age did not retain the diagnosis at 7 years, although
many of these false positives did have other neurodevelopmental disorders including mental retardation, seizures, speech articulation problems, and hyperactivity. Thus, the neurological examination alone, primarily a measure of impairment in the early months, is insufficiently sensitive or specific for effective early diagnosis of CP. Refinements, including the additional assessment of primitive reflexes and postural responses, offer some help, but do not resolve the basic difficulties with sensitivity and specificity.

FUNCTIONAL LIMITATIONS

Cerebral palsy is a disorder of movement and postural control that results in functional limitations. It is these functional limitations and their effects on day-to-day activities that become the disability that is CP. Impairment noted on examination, but which does not lead to limited function, will not result in disability. Hence, a diagnostic strategy that focuses on identifying functional limitations may offer benefits over strategies that identify impairment only.

The most straightforward approach to identify functional limitations is based on rate of motor development as defined by motor quotient (motor quotient = motor age/chronological age, with motor age determined by best motor milestone performance). A motor quotient <.5 at 8 months of age predicts delayed age of walking (>24 months), with a sensitivity of 87% and specificity of 89%. This degree of sensitivity and specificity does not hold at 6 months of age or earlier, however, possibly because of the paucity of traditional motor milestones in the first 6 months of life. The addition of neuromotor examination findings (primitive reflexes) to a milestone performance measure (delayed rolling) to form a two-stage screening instrument may result in somewhat earlier detection of motor abnormality with similar sensitivity and specificity, but is not likely to be a significant improvement over the motor quotient, especially in children with mild CP.

Recently, objective assessment of videotaped spontaneous general movements has been shown to be predictive of later CP. Most importantly, these measures are sensitive and specific in the first weeks and months of life, at an age when the neurological examination is insensitive and a motor quotient is impractical because of limited traditional functional motor milestones. This technique, discussed elsewhere in this supplement (Hadders-Algra M. J Pediatr 2004;145:S12–S18), is based on careful observation of the maturation of spontaneous general movements from soon after birth, even in the preterm infant, to 16 to 20 weeks’ term age equivalent. The predominance of cramped, synchronous general movements and, to a lesser extent, the absence of normal fidgety movements of the limbs, neck, and trunk during these early weeks is predictive of abnormality. In a sample of 84 preterm infants, abnormalities in general movements in the first 16 to 20 weeks postterm predicted CP at age 2 to 3 years with a sensitivity of 100% and a specificity of 92.5% to 100%. Further, the technique predicted severity of motor delay: the earlier the abnormalities were recognized, the more severe the later limitations in motor function. This improved ability to predict neuromotor functional outcome over measures that focus primarily on impairment (the neurological examination) is not surprising. Spontaneous general movements are the best expression of functional motor development at this early age and are analogous with the later more familiar functional motor milestones. Thus, observed abnormal neuromotor function early on predicts later abnormal neuromotor function—cerebral palsy.

Although the general utility of objective measurement of spontaneous general movements in high-risk newborn follow-up programs requires further study, it is likely that clinicians involved in care of such infants can improve their clinical skills and recognition of abnormality by careful attention to these movements. It will also be important to evaluate how these techniques can be used to complement the currently standard head ultrasound protocols in developing longer-term neurodevelopmental prognosis.

Strategies for early detection and diagnosis of CP will continue to require recognition of abnormalities related to pathogenesis, impairment, and function. Although certain measures are better individual predictors of CP, a comprehensive clinical approach requires some attention to multiple measures. Organized follow-up programs in high-risk infants with low birth weight should rely on neuroimaging findings supplemented by prenatal and neonatal indicators of risk and sequential examination, including attention to spontaneous general movements. Term infants without neonatal encephalopathy who eventually develop CP are usually not seen as high-risk neonates. Primary care–based developmental surveillance and referral to a neurodevelopmental specialist, if indicated, will be necessary to detect and diagnose CP in these infants. Monitoring early neuromotor development in the term infant, with special attention to emerging functional limitations expressed as motor delay, undergirds these efforts.

REFERENCES