Encephalopathies

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Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive, or static. The etiologies of the encephalopathies in children include infectious, toxic (carbon monoxide, drugs, lead), metabolic, genetic, and ischemic causes. Hypoxic–ischemic encephalopathy is discussed in Chapter 99.5.

Cerebral Palsy

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See Chapters 36, 97.2, and 597.3.

Cerebral palsy (CP) is a diagnostic term used to describe a group of permanent disorders of movement and posture causing activity limitation, that are attributed to nonprogressive disturbances in the in the developing fetal or infant brain. The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as by epilepsy and secondary musculoskeletal problems. CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other acquired etiologies that produce a common group of neurologic phenotypes. CP has historically been considered a static encephalopathy, but some of the neurologic features of CP, such as movement disorders and orthopedic complications, including scoliosis and hip dislocation, can change or progress over time. Many children and adults with CP function at a high educational and vocational level, without any sign of cognitive dysfunction.

Epidemiology and Etiology

CP is the most common and costly form of chronic motor disability that begins in childhood; data from the Centers for Disease Control and Prevention indicate that the incidence is 3.6 per 1,000 children with a male : female ratio of 1.4 : 1. The Collaborative Perinatal Project, in which approximately 45,000 children were regularly monitored from in utero to the age of 7 yr, found that most children with CP had been born at term with uncomplicated labors and deliveries. In 80% of cases, features were identified pointing to antenatal factors causing abnormal brain development. A substantial number of children with CP had congenital anomalies external to the central nervous system (CNS). Fewer than 10% of children with CP had evidence of intrapartum asphyxia. Intrauterine exposure to maternal infection (chorioamnionitis, inflammation of placental membranes, umbilical cord inflammation, foul-smelling amniotic fluid, maternal sepsis, temperature >38°C [100.4°F] during labor, urinary tract infection) was associated with a significant increase in the risk of CP in normal birthweight infants. Elevated levels of inflammatory cytokines have been reported in heelstick blood collected at birth from children who later were identified with CP. Genetic factors may contribute to the inflammatory cytokine response, and a functional polymorphism in the interleukin-6 gene is associated with a higher rate of CP in term infants.
The prevalence of CP has increased somewhat as a result of the enhanced survival of very premature infants weighing <1,000 g, who go on to develop CP at a rate of approximately 15 per 100. However, the gestational age at birth-adjusted prevalence of CP among 2 yr old former premature infants born at 20-27 wk of gestation has decreased over the past decade. The major lesions that contribute to CP in preterm infants are intracerebral hemorrhage and periventricular leukomalacia (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 wk of gestational age among former preterm infants are a predictor of later CP.

In 2006, the European Cerebral Palsy Study examined prenatal and perinatal factors as well as clinical findings and results of MRI in a contemporary cohort of more than 400 children with CP. In agreement with the Collaborative Perinatal Project study, more than half the children with CP in this study were born at term, and less than 20% had clinical or brain imaging indicators of possible intrapartum factors such as asphyxia. The contribution of intrapartum factors to CP is higher in some underdeveloped regions of the world. Also in agreement with earlier data, antenatal infection was strongly associated with CP and 39.5% of mothers of children with CP reported having an infection during the pregnancy, with 19% having evidence of a urinary tract infection and 11.5% reporting taking antibiotics. Multiple pregnancy was also associated with a higher incidence of CP and 12% of the cases in the European CP study resulted from a multiple pregnancy, in contrast to a 1.5% incidence of multiple pregnancy in the study. Other studies have also documented a relationship between multiple births and CP, with a rate in twins that is 5-8 times greater than in singleton pregnancies and a rate in triplets that is 20-47 times greater. Death of a twin in utero carries an even greater risk of CP that is 8 times that of a pregnancy in which both twins survive and approximately 60 times the risk in a singleton pregnancy. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. Among children from multiple pregnancies, 24% were from pregnancies after infertility treatment compared with 3.4% of the singleton pregnancies in the study. CP is more common and more severe in boys compared to girls and this effect is enhanced at the extremes of body weight. Male infants with intrauterine growth retardation and a birthweight less than the 3rd percentile are 16 times more likely to have CP than males with optimal growth, and infants with weights above the 97th percentile are 4 times more likely to have CP.

Clinical Manifestations

CP is generally divided into several major motor syndromes that differ according to the pattern of neurologic involvement, neuropathology, and etiology (Table 598-1). The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities. CP is also commonly associated with a spectrum of developmental disabilities, including intellectual
impairment, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities. The motor handicap may be the least of the child's problems.

Table 598-1
Classification of Cerebral Palsy and Major Causes

<table>
<thead>
<tr>
<th>MOTOR SYNDROME (APPROX. % OF CP)</th>
<th>NEUROPATHOLOGY/MRI</th>
<th>MAJOR CAUSES</th>
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</table>
| Spastic diplegia (35%)           | Periventricular leukomalacia  
Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles | Prematurity  
Ischemia  
Infection  
Endocrine/metabolic (e.g., thyroid) |
| Spastic quadriplegia (20%)       | Periventricular leukomalacia  
Multicystic encephalomalacia  
Cortical malformations | Ischemia, infection  
Endocrine/metabolic, genetic/developmental |
| Hemiplegia (25%)                 | Stroke: in utero or neonatal  
Focal infarct or cortical, subcortical damage  
Cortical malformations | Thrombophilic disorders  
Infection  
Genetic/developmental  
Periventricular hemorrhagic infarction |
| Extrapyramidal (athetoid, dyskinetic) (15%) | Asphyxia: symmetric scars in putamen and thalamus  
Kernicterus: scars in globus pallidus, hippocampus  
Mitochondrial: scaring globus pallidus, caudate, putamen, brainstem  
No lesions: ? dopa-responsive dystonia | Asphyxia  
Kernicterus  
Mitochondrial  
Genetic/metabolic |

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Infants with **spastic hemiplegia** have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 yr of age.
Walking is usually delayed until 18-24 mo, and a circumductive gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe because of the increased tone in the antigravity gastrocnemius muscles, and the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. About one-third of patients with spastic hemiplegia have a seizure disorder that usually develops in the 1st yr or 2; approximately 25% have cognitive abnormalities including mental retardation. MRI is far more sensitive than CT for most lesions seen with CP, although a CT scan may be useful for detecting calcifications associated with congenital infections. In the European CP study, 34% of children with hemiplegia had injury to the white matter that probably dated to the in utero period and 27% had a focal lesion that may have resulted from a stroke. Other children with hemiplegic CP had had malformations from multiple causes including infections (e.g., cytomegalovirus), lissencephaly, polymicrogyria, schizencephaly, or cortical dysplasia. Focal cerebral infarction (stroke) secondary to intrauterine or perinatal thromboembolism related to thrombophilic disorders, like the presence of anticardiolipin antibodies, is an important cause of hemiplegic CP (see Chapter 601). Family histories suggestive of thrombosis and inherited clotting disorders, such as factor V Leiden mutation, may be present and evaluation of the mother may provide information valuable for future pregnancies and other family members.

**Spastic diplegia** is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with damage to the immature white matter during the vulnerable period of immature oligodendroglia between 20-34 wk of gestation. However, approximately 15% of cases of spastic diplegia result from in utero lesions in infants who go on to delivery at term. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal 4-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. If there is paraspinal muscle involvement, the child may be unable to sit. Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoe. Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development for these patients is good, and the likelihood of seizures is minimal. Such children often have learning disabilities and deficits in other abilities, such as vision, because of disruption of multiple white matter pathways that carry sensory as well as motor information.
The most common neuropathologic finding in children with spastic diplegia is PVL, which is visualized on MRI in more than 70% of cases. MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles. However, neuropathology has also demonstrated a reduction in oligodendroglia in more widespread subcortical regions beyond the periventricular zones, and these subcortical lesions may contribute to the learning problems these patients can have. MRI with diffusion tensor imaging is being used to map white matter tracks more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 598-1). These observations have led to greater interest in the importance of sensory deficits in these patients, which may be important for designing rehabilitative techniques.

**Spastic quadriplegia** is the most severe form of CP because of marked motor impairment of all extremities and the high association with intellectual disability and seizures. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia. The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees and elbows are often present by late childhood. Associated developmental disabilities, including speech and visual abnormalities, are particularly prevalent in this group of children. Children with spastic quadriparesis often have evidence of athetosis and may be classified as having mixed CP.

**Athetoid CP**, also called **choreoathetoid**, **extrapyramidal**, or **dyskinetic** CP, is less common than spastic CP and makes up approximately 15-20% of patients with CP. Affected infants are characteristically hypotonic with poor head control and marked head lag and develop variably increased tone with rigidity and dystonia over several years. The term *dystonia* refers to the abnormality in tone in which muscles are rigid throughout their range of motion and involuntary contractions can occur in both flexors and extensors leading to limb positioning in fixed postures. Unlike spastic diplegia, the upper extremities are generally more affected than the lower extremities in extrapyramidal CP. Feeding may be difficult, and tongue thrust and drooling may be prominent. Speech is typically affected because the oropharyngeal muscles are involved. Speech may be absent or sentences are slurred, and voice modulation is impaired. Generally, upper motor neuron signs are not present, seizures are uncommon, and intellect is preserved in many patients. This form of CP is also referred to in Europe as dyskinetic CP and is the type most likely to be associated with *birth asphyxia*. In the European CP study, 76% of patients with this form of CP had lesions in the basal ganglia and thalamus. Extrapyramidal CP secondary to acute intrapartum near-total asphyxia is associated with bilaterally symmetric lesions in the posterior putamen and ventrolateral thalamus. These lesions appear to be the correlate of the neuropathologic lesion called *status marmoratus* in the basal ganglia. Athetoid CP can also be caused by *kernicterus* secondary to high levels of bilirubin, and in this case the MRI scan shows lesions in the globus pallidus bilaterally. Extrapyramidal CP can also be
associated with lesions in the basal ganglia and thalamus caused by metabolic genetic
disorders such as mitochondrial disorders and glutaric aciduria. MRI scanning and
possibly metabolic testing are important in the evaluation of children with
extrapyramidal CP to make a correct etiologic diagnosis. In patients with dystonia who
have a normal MRI, it is important to have a high level of suspicion for
dihydroxyphenylalanine (DOPA)-responsive dystonia (Segawa disease), which causes
prominent dystonia that can resemble CP. These patients typically have diurnal
variation in their signs with worsening dystonia in the legs during the day; however, this
may not be prominent. These patients can be tested for a response to small doses of L-
dopa and/or cerebrospinal fluid can be sent for neurotransmitter analysis.

Associated comorbidities are common and include pain (in 75%), cognitive disability
(50%), hip displacement (30%), seizures (25%), behavioral disorders (25%), sleep
disturbances (20%), visual impairment (19%), and hearing impairment (4%).

Diagnosis

A thorough history and physical examination should preclude a progressive
disorder of the CNS, including degenerative diseases, metabolic disorders, spinal cord
tumor, or muscular dystrophy. The possibility of anomalies at the base of the skull or
other disorders affecting the cervical spinal cord needs to be considered in patients with
little involvement of the arms or cranial nerves. An MRI scan of the brain is indicated to
determine the location and extent of structural lesions or associated congenital
malformations; an MRI scan of the spinal cord is indicated if there is any question about
spinal cord pathology. Additional studies may include tests of hearing and visual
function. Genetic evaluation should be considered in patients with congenital
malformations (chromosomes) or evidence of metabolic disorders (e.g., amino acids,
organic acids, MR spectroscopy). In addition to the genetic disorders mentioned earlier
that can present as CP, the urea cycle disorder arginase deficiency is a rare cause of
spastic diplegia and a deficiency of sulfite oxidase or molybdenum cofactor can present
as CP caused by perinatal asphyxia. Tests to detect inherited thrombophilic disorders
may be indicated in patients in whom an in utero or neonatal stroke is suspected as the
cause of CP.

Because CP is usually associated with a wide spectrum of developmental disorders, a
multidisciplinary approach is most helpful in the assessment and treatment of such
children.

Treatment

Some progress has been made in both prevention of CP before it occurs and treatment
of children with the disorder. Preliminary results from controlled trials of magnesium
sulfate given intravenously to mothers in premature labor with birth imminent before
32 wk gestation showed significant reduction in the risk of CP at 2 yr of age.
Nonetheless, one study that followed preterm infants whose mothers received
magnesium sulfate demonstrated no benefit in terms of the incidence of CP and
abnormal motor, cognitive, or behavioral function at school age. Furthermore, several
large trials have shown that cooling term infants with hypoxic–ischemic encephalopathy
to 33.3°C (91.9°F) for 3 days, starting within 6 hr of birth, reduces the risk of dyskinetic or spastic quadriplegia form of CP.

For children who have a diagnosis of CP, a team of physicians, including neurodevelopmental pediatricians, pediatric neurologists, and physical medicine and rehabilitation specialists, as well as occupational and physical therapists, speech pathologists, social workers, educators, and developmental psychologists, is important to reduce abnormalities of movement and tone and to optimize normal psychomotor development. Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that limit the effects of abnormal muscle tone. They also need to be instructed in the supervision of a series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon. Physical and occupational therapies are useful for promoting mobility and the use of the upper extremities for activities of daily living. Speech language pathologists promote acquisition of a functional means of communications. These therapists help children to achieve their potential and often recommend further evaluations and adaptive equipment.

Children with spastic diplegia are treated initially with the assistance of adaptive equipment, such as walkers, poles, and standing frames. If a patient has marked spasticity of the lower extremities or evidence of hip dislocation, consideration should be given to performing surgical soft-tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release. A rhizotomy procedure in which the roots of the spinal nerves are divided produces considerable improvement in selected patients with severe spastic diplegia (Fig. 598-2). A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon. Quadriplegia is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrangements. The function of the affected extremities in children with hemiplegic CP can often be improved by therapy in which movement of the good side is constrained with casts while the impaired extremities perform exercises which induce improved hand and arm functioning. This constraint-induced movement therapy is effective in patients of all ages.

Several drugs have been used to treat spasticity, including the benzodiazepines and baclofen. These medications have beneficial effects in some patients but can also cause side effects such as sedation for benzodiazepines and lowered seizure threshold for baclofen. Several drugs can be used to treat spasticity, including oral diazepam (0.01-0.3 mg/kg/day, divided bid or qid), baclofen (0.2-2 mg/kg/day, divided bid or tid) or dantrolene (0.5-10 mg/kg/day, bid). Small doses of levodopa (0.5-2 mg/kg/day) can be
used to treat dystonia or DOPA-responsive dystonia. Artane (trihexyphenidyl, 0.25 mg/day, divided bid or tid and titrated upward) is sometimes useful for treating dystonia and can increase use of the upper extremities and vocalizations. Reserpine (0.01-0.02 mg/kg/day, divided bid to a maximum of 0.25 mg daily) or tetrabenazine (12.5-25.0 mg, divided bid or tid) can be useful for hyperkinetic movement disorders including athetosis or chorea.

Intrathecal baclofen delivered with an implanted pump has been used successfully in many children with severe spasticity, and can be useful because it delivers the drug directly around the spinal cord where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood–brain barrier. This therapy requires a team approach and constant follow-up for complications of the infusion pumping mechanism and infection. Botulinum toxin injected into specific muscle groups for the management of spasticity shows a very positive response in many patients. Botulinum toxin injected into salivary glands may also help reduce the severity of drooling, which is seen in 10-30% of patients with CP and has been traditionally treated with anticholinergic agents. Patients with rigidity, dystonia, and spastic quadriplegia sometimes respond to levodopa, and children with dystonia may benefit from carbamazepine or trihexyphenidyl. Hyperbaric oxygen has not been shown to improve the condition of children with CP.

Communication skills may be enhanced by the use of Bliss symbols, talking typewriters, electronic speech generating devices, and specially adapted computers including artificial intelligence computers to augment motor and language function. Significant behavior problems may substantially interfere with the development of a child with CP; their early identification and management are important, and the assistance of a psychologist or psychiatrist may be necessary. Learning and attention deficit disorders and mental retardation are assessed and managed by a psychologist and educator. Strabismus, nystagmus, and optic atrophy are common in children with CP; an ophthalmologist should be included in the initial assessment. Lower urinary tract dysfunction should receive prompt assessment and treatment.

Bibliography