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Etiology, Epidemiology, Pathology, and Diagnosis

Cerebral palsy (CP) is a static lesion occurring in the immature brain that leaves children with a permanent motor impairment. The lesion may occur as a developmental defect, such as lissencephaly; as an infarction, such as a middle cerebral artery occlusion in a neonate; or as trauma during or after delivery. Because brain pathology in all these etiologies is static, it is considered CP. Many minor static lesions leave no motor impairment and do not cause CP. Many pathologies, such as Rett syndrome, are progressive in childhood, but then become static at or after adolescence. These conditions are not part of the CP group, but after they become static, they have problems very similar to those of CP from the motor perspective. Other problems, such as progressive encephalopathy, have very different considerations from the motor perspective.

Saying a child has CP only means the child has a motor impairment from a static brain lesion, but says nothing about the etiology of this impairment. Some authors advocate using a plural term of "cerebral palsies" to imply that there are many kinds of CP.[1] There is some validity to this concept, similar to the term "cancer," in which many specific pathologic types of cancer, each with a different treatment, are recognized. Although applying this concept to CP is appealing from the perspective of determining etiologies and understanding the epidemiology, it provides very little help in actually managing the motor impairment. From the cancer analogy, for example, the specific cellular type and stage of breast cancer are important to know to prescribe the correct treatment. With CP, knowing the cause does not help treat a child who has a dislocated hip. The treatment is based on the diagnosis of CP, as opposed to a muscle disease, spinal paralysis, or a progressive encephalopathy. The original cause of the CP does not matter. Therefore, the concept of "cerebral palsies" is not used in the remainder of this text, and the term cerebral palsy will not carry any information on specific etiology. Although the etiologic information has little relevance in the management of motor impairments, it is of limited importance in some children for giving a prognosis. The etiology can be important to families in terms of genetic counseling with respect to the risks of future pregnancies, and it is important as an outcome measure for nurseries and epidemiology.

Physicians who manage the motor impairments must always maintain a healthy suspicion of the diagnosis of CP, as sometimes a dual diagnosis may be present or the original diagnosis may be wrong. When progression of the impairments and disability, along with a child's maturity, do not fit the usual pattern of CP, more workup is indicated. For example, a child may be diagnosed with diplegia because he was premature and had an intraventricular hemorrhage, but, by age 6 years, the physical examination demonstrated very

large calves with much more weakness and less spasticity than would usually be expected. This child would need to be worked up for muscle disease with the understanding that he can have both Duchenne's muscular dystrophy and diplegic pattern CP. Alternatively, the child's history may have been a red herring and he does not have CP, but does have Duchenne's muscular dystrophy. There are children born prematurely who have intraventricular hemorrhages but are completely normal from a motor perspective.

Etiology of Cerebral Palsy

As noted previously, there are many causes of CP, and knowing the exact etiology is not very important for a physician managing the motor impairments. The etiology may be important when considering whether a child is following an expected course of maturation and development. Also, parents find the etiology important because it is part of coming to terms with the larger question of why the CP happened. Many etiologies can be separated into a time period as to when these insults occurred. For more detailed information on the etiologies of CP, readers are referred to the book *The Cerebral Palsies* by Miller and Clarke,[1] which provides much greater detail on this specific topic.

Congenital Etiologies

A whole group of congenital developmental deformities lead to CP. These deformities result from defects that occur in normal development and follow patterns based on failures of normal formation (Figure 2.1). A defect of the neural tube closure is the earliest recognized deformity leading to survival with motor defects. The most common neural tube defect occurs in the spine and is known as meningomyelocele. However, this lesion typically does not cause CP, but instead causes spinal-level paralysis. In the brain, the neural tube defect is called an encephalocele, and may be anterior, with a major midface or nasal defect. Anterior encephaloceles occurs most commonly in Asia, whereas posterior encephaloceles most often occur in Western Europe and America and affect the posterior occiput.[1] The cause of this regional difference is unknown; however, just as folate used during pregnancy has been found to protect against myelomeningocele development, it is believed to protect against the development of encephalocele as well.[1–3] Some encephaloceles are related to larger syndromes, such as Meckel's syndrome.[4] This syndrome includes encephalocele with microcephaly, renal dysplasia, and polydactyly and is due to a defect on the 17th chromosome, specifically in the homeobox gene (HOX B6). This information suggests that many of these deformities may have unrecognized genetic causes. Most children with significant encephaloceles have very significant motor impairments, usually quadriplegic pattern involvement with more hypotonia than hypertonia.

Segmental defects in the brain are called schizencephaly, meaning there is a cleft in the brain.[5] These schizencephalies vary greatly, from causing minimal disability to causing very severe quadriplegic pattern involvement, usually with spasticity and mental retardation. Several patients with severe forms have genetic defects in the homeobox genes.

Primary proliferation defects of the brain lead to microencephaly. However, there are many causes of microencephaly, most involving toxins or infections, which are discussed later. Conditions in which the brain is too large are called megaloencephaly, which should not be confused with macroencephaly, meaning a head that is too large. Megaloencephaly is caused by

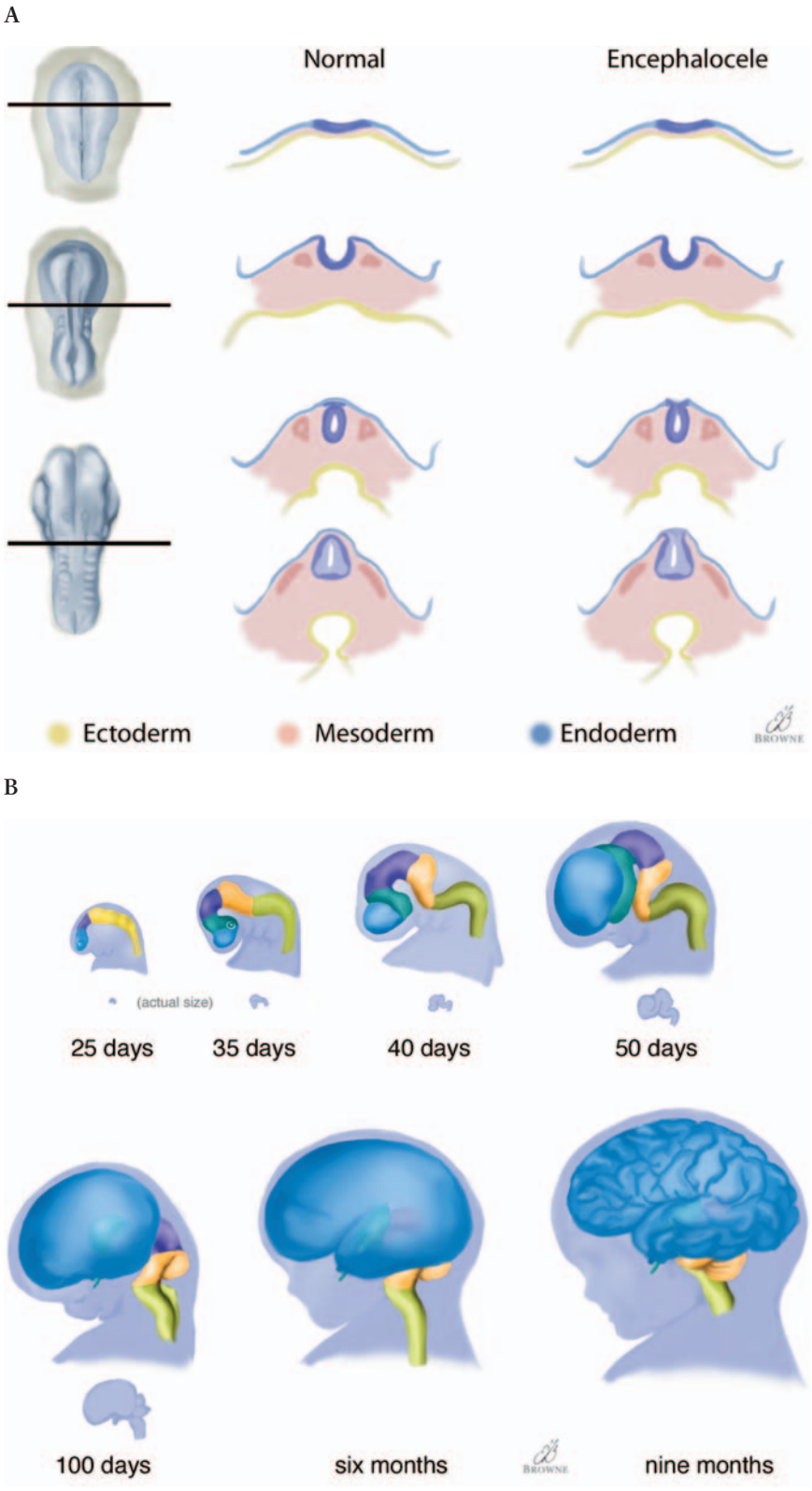


Figure 2.1. In the earliest stage, the neural plate differentiates from the ectoderm, then enfolds to create a neural tube. Failure of this enfolding causes neural tube defects (A). During the embryonic stage, this neural tube develops complex folding with the formation of flexures. During the period of 30 to 100 days of embryonic life, the brain demarcates and develops the cerebral hemispheres. During the rest of gestation, there is a large growth of mass and cell specialization (B).

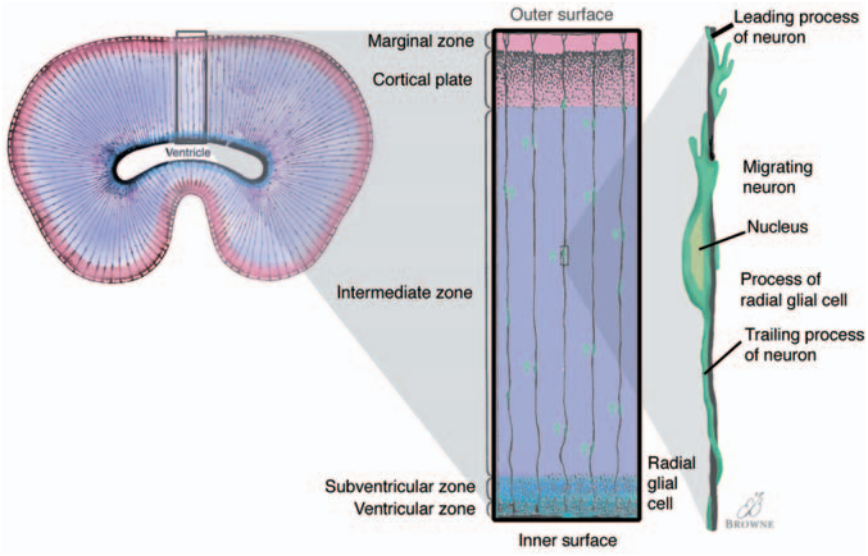


Figure 2.2. As the brain matures, the cells proliferate centrally and migrate toward the cortex. During this migration, trailing connections remain to the deep layer. This migration is an important element in the formation of the gyri of the cerebral cortex. Defects in the migration lead to a smooth brain surface called lissencephaly.

cellular hyperproliferation, usually in syndromes such as sebaceous nevus syndrome, whereas macrocephaly most often is due to hydrocephalus.

During development, the neurons migrate toward the periphery of the brain, and a defect in this migration pattern leads to lissencephaly, meaning a smooth brain, or a child with decreased cerebral gyri. Lissencephaly usually leads to severe spastic quadriplegic pattern involvement, but there is a significant range of involvement. Lissencephaly is X-linked in a few cases. The opposite of too few gyri seen in lissencephaly is polymicrogyria, in which there are too many small gyri (Figure 2.2).[1]

A large and variable group of children have differing degrees of cortical dysgenesis, which is a disorder of brain cortex formation. This disorder may be called focal cortical dysplasia and presents mainly with seizure disorders. The motor effects may vary from none to very severe and from hypotonia to hypertonia.

Another part of normal development of the brain in the neonatal and prenatal period requires formation of the synapses and then subsequent remodeling of this neuronal synapse formation. As the cells migrate into the correct position and initially form their synapses, many of these premature synapses need to be remodeled through the influence of external stimuli for normal function to develop. The classic demonstration of this principle was shown in the experiment in which eyes of kittens, one each kitten, were sewn closed at birth. The eye that was denied light stimulation became cortically blind; however, the opposite eye that did get light and normal stimulation became overrepresented in the cortex of the brain.[6] This experiment has become the basis for treating and understanding amblyopia, or lazy eye, in children. The synaptic remodeling and formation, also called synaptic plasticity in older ages, continues throughout life and is the basis for much of learning. The nature of this synaptic remodeling potential changes with age as demonstrated by the example with the kittens. If the kitten whose eye was sewn shut is denied light stimulation until a certain age, it can no longer recover the ability for sight in that eye.[6]

This concept of synaptic formation and remodeling has been the basis of some therapy programs, specifically the patterning therapy proposed by Doman and Delacatta.[6–8] There is no scientific evidence to suggest that the human gait generator can be accessed and impacted in the same way one can

treat lazy eye at an early age in children. However, there is a general understanding that significant seizure activity in a young child may prevent synaptic remodeling through excitotoxic injury, which leads to CP. Inappropriate synaptic formation and remodeling, or remodeling alone, has been implicated as the major neurologic anatomic pathology in Down syndrome, Rett syndrome, autism, and fragile X syndrome as well as many cases of ataxia, idiopathic spasticity, and mental retardation in which there is no other recognized etiology.[1]

Neonatal Etiologies

Neonatal and prenatal causes of CP are mainly related to prematurity and birthing problems, which lead to various injury patterns. However, the immature brain has much more equipotentiality or plasticity, both of which are terms used to define the much greater ability of an uninjured part of the immature brain to assume the function of an injured part. This potential of the immature brain to reassign function makes the response to injury much different than in the mature brain.

Prematurity and brain hemorrhages are much better understood since the widespread use of cranial ultrasound, in which the infant brain can be imaged through the open anterior fontanelle. This image provides an excellent view of the ventricles and the periventricular white matter. This is the area where hemorrhages occur, and major risk factors for developing hemorrhages are younger gestational age and mechanical ventilation. Bleeding in the ventricle is called intraventricular hemorrhage (IVH), and bleeding in the periventricular area is called germinal matrix hemorrhage (GMH), or it may be combined in a term called periventricular-intraventricular hemorrhage (PIVH). A common grading system for the severity of these hemorrhage patterns includes grade I with germinal matrix hemorrhage only, grade II with hemorrhage in the lateral ventricle and dilation of the lateral ventricle, grade III with ventricular system enlargement, and grade IV with periventricular hemorrhage and infarctions (Figure 2.3). Reported prognostic significance of these grades varies greatly, and the general consensus is that premature infants with no PIVH have a better survival prognosis than those with PIVH.[1] Also, in group studies, the more severe the grade, the higher the risk of developing CP, as demonstrated in a study that reported the risk of CP was 9% in grade I, 11% in grade II, 36% in grade III, and 76% in grade IV.[9] However, different studies vary significantly, so good consensus values are not currently available.

These cerebral hemorrhages evolve from GMH and IVH, which develop in the first 72 hours after birth. The brain bleeds then resolve, and periventricular leukomalacia (PVL) develops 1 to 3 weeks after birth in some children. Periventricular leukomalacia in the form of periventricular echogenicity (PVE) may be seen on ultrasound, but does not develop cysts. If cysts develop, it is called cystic periventricular leukomalacia (PVC). In general, infants with PVC have the highest risk of developing CP and infants with PVE have the lowest risk.[10] In one study, 10% of children developed CP if they had PVE; however, 65% developed CP if they had PVC.[9] Again, these numbers vary between studies. The general trend is that premature infants with more severe bleeds have a worse prognosis for survival and a higher risk for developing CP; however, there are no specific parameters that fully predict risk of developing CP or, much less, predict the severity of CP in an individual child.

Hypoxic events occurring around delivery, usually in full-term infants, also lead to disability. These events have been termed hypoxic-ischemic

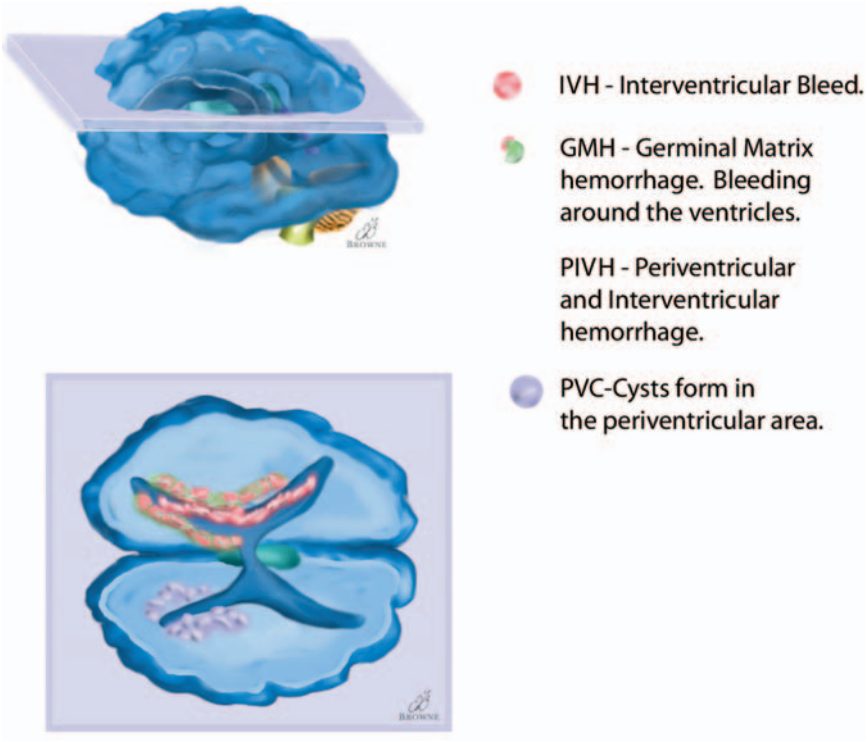


Figure 2.3. Bleeding in the immature brain occurs primarily around the ventricles, which have many fragile vessels. Intraventricular hemorrhage (IVH) means bleeding into the ventricles. Germinal matrix hemorrhage (GMH) means bleeding into the tissue around the ventricles. Periventricular intraventricular hemorrhage (PIVH) means bleeding into both areas. Periventricular cysts (PVC) form in these same areas as the acute hemorrhage resolves.

encephalopathy (HIE). The causes of this hypoxia may vary from obstetric dystocias to other anoxic and low-flow states in the neonate. In severe cases of HIE, subcortical cyst formation develops and is called multicystic encephalomalacia. In general, when this cystic pattern forms, the prognosis for good function is poor, with most of these children developing severe quadriplegic pattern involvement with severe mental retardation. Some of these children develop cysts in the thalamus and basal ganglia, which may lead to dystonia.[1]

Neonatal stroke occurring in the preterm or full-term infant usually involves the middle cerebral artery and presents as a wedge-shaped defect in one hemisphere. These defects may develop as cysts, which, if very large, are called porencephaly or porencephalic cysts. In general, if these wedge-shaped defects are small, the children may be normal; however, a significant defect especially with a cyst usually presents as hemiplegic pattern CP. Even with large cysts, these children's function, especially cognitive function, may be quite good.

Postnatal Causes of Cerebral Palsy

Postnatal causes of CP may overlap somewhat with the prenatal and neonatal group; however, postnatal trauma, metabolic encephalopathy, infections, and toxicities are considered as etiologies in this group. Although the data are difficult to assimilate, between 10% and 25% of CP cases have a postnatal cause.[11,12]

Child abuse or nonaccidental trauma causing brain injury in a young child may be due to blunt trauma with skull fractures or fall into the pattern of shaken baby syndrome. Shaken baby syndrome occurs usually in a child less than 1 year of age when a caretaker shakes the baby back and forth to quiet the crying. This vigorous shaking causes stretching, shearing, and tear-

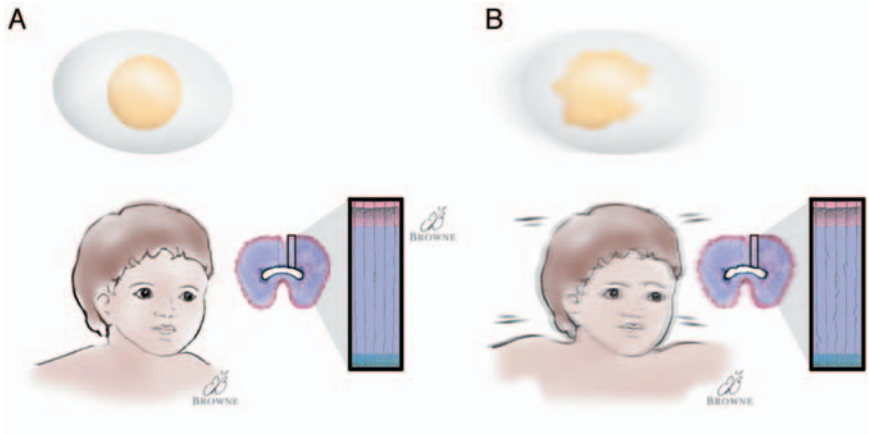


Figure 2.4. Shaken baby syndrome creates an injury in which axons are disrupted by the shear forces created from the violent shaking of the head. The brain of the baby is like an egg in which the liquid center is enclosed in a solid outer shell. By vigorous shaking, the egg yolk can be broken without breaking the shell of the egg. In the same way, vigorous shaking of a baby's head can cause tissue disruption. This shearing stress disrupts brain tissue, especially the long migrating axons of the cerebral cortex. The trauma of the shaken baby does not usually cause a skull fracture and may not even cause intracranial bleeding, but it often causes severe long-term neurologic impairment because of the cellular disruptions.

ing of the long axons and capillaries in the cortex of the brain (Figure 2.4). If these babies survive, they often have a severe spastic quadriplegic pattern involvement with a poor prognosis for improvement.[5] Even children with less severe motor involvement often have a concomitant profound mental retardation.

Blunt head trauma may also occur from child abuse, falls, or motor vehicle accidents, and it involves the direct injury as well as the secondary injury from brain swelling. Most children with blunt trauma recover and have no motor defects.[13] However, if there is a unilateral bleed, these children are often left with a hemiplegic pattern motor disability. The more severely involved children are usually left with a severe quadriplegic pattern involvement and do not become functional community ambulators. Many children with motor impairments from closed head injuries have ataxia as a major impairment.

Children with closed head injuries will make substantial improvement for 1 year after the injury and only in rare severe cases should surgical treatment of secondary problems, such as contractures, be considered during this year. Also, many children continue to improve even through the third year after injury; therefore, it is probably best not to consider the lesion static until 3 years after the injury.[14] Even then, these lesions continue to evolve in some individuals, with the well-recognized syndrome in which early spasticity resolves but then dystonic movements later develop in the previously spastic limb. This syndrome has been reported to occur up to 9 years after closed head injury, even when it seemed that all the spasticity had resolved.[15] We have seen recurrent dystonia become most severe during and after puberty, as the hormonal surge somehow makes it worse.

Metabolic encephalopathy has a wide variety of causes, most extremely rare. It is impossible to give a comprehensive review in this text, and when specific cases are encountered, it is important to obtain disease-specific up-to-date recommendations from the subspecialized expert who is managing the care of the child. Also, the neuro-orthopaedist should have a good reference text available, such as the Aicardi text *Diseases of the Nervous System in Childhood*.[16] The metabolic disorders can be divided into storage disorders, intermedullary metabolism disorders, metallic metabolism, and miscellaneous disorders (Table 2.1).

It is extremely important for physicians caring for children's motor problems to understand the expected course of the disease. For example, many of the storage disorders are progressive and these children have limited life expectancy, which limits attempts to correct motor impairments that are not

Table 2.1. Metabolic neurologic diseases.

Name	Primary defect	Typical course	Significance for surgical management
Storage diseases	intercellular accumulation	Most of these have no treatment and are progressive	
Gangliosidoses	Hexosaminidase defect, multiple types	Each type has its own course	
Tay–Sachs disease	HexA and HexB nonfunctional due to chromosome 15 defect	Short-term survival in childhood	
Sandhoff's disease	Type O gangliosidosis	Clinically like Tay–Sachs	
GM1 gangliosidosis	Multiple subtypes, beta-galactosidase deficiency	Rare cases and variable effects	
Gaucher's disease	Multiple types, beta-glucocerebrosidase deficient	Outcome is variable, based on the subtype, from rapid course with death in early childhood to relatively mild involvement	Most patients have hepatosplenomegly Be especially aware of significant splenomegly Also, bone lesion from the storage disease may be present
Niemann–Pick disease	Sphingomyelinase deficient, multiple subtypes	The more severe types have rapid degeneration and death; some mild types may have minimal involvement and life into middle adulthood	Bone marrow may be involved, and some patients develop a peripheral neuropathy
Fabry's disease	Sex-linked deficiency of ceramide trihexoside	Foam cells with vacuolated cytoplasm develop in muscles, nervous system, kidneys	Death is usually from cardiac or renal failure Females are less affected May begin as severe muscle pain Renal failure may occur
Metachromatic leukodystrophy	Cerebroside sulfatase deficiency, multiple types	Often presents as a gait disorder in childhood May initially look like a neuropathy Adult forms present as behavior problems	
Krabbe's disease (globoid cell leukodystrophy)	Beta-galactocerebrosidase deficiency	Age of onset, and survival, are variable	May present with slow-onset hemiplegia or diplegia
Mucopolysaccharidosis	All have deficiencies of lysomal glucosidase or sulfatase	Often the neurologic problems are less severe than the systemic ones	Bone marrow transplantation is used to treat a number of these conditions
Hurler's syndrome	—	Severe neurologic retardation	Severe dwarfism Cervical instability
Scheie's syndrome	—	Types, very mild to minimal problems	Hydrocephalus may develop
Hunter's syndrome	—	Severe dwarfism	Mild to moderate neurologic involvement
Sanfilippo's syndrome	—	Severe progressive neurologic involvement	Minimal skeletal problems
Morquio's syndrome	—	Variable forms but marker bone involvement	Cervical instability may cause spinal cord compression
Maroteaux–Lamy's syndrome	—	No neurologic involvement Severe dwarfism	Nerve entrapment syndromes are common Mild to severe bone and neurologic involvement
Sly's syndrome	—	Very variable	Mild to severe bone and neurologic involvement
Mucolipidosis, sialidosis, glycoprotein metabolism deficiency		Many types, all very rare	
Sialidosis type one	Also called cherry red spot myoclonus syndrome	Slow progression No other involvement	Late onset Has a pure intention myoclonus that slowly gets worse with age
Mucolipidosis IV	—	Failing vision and mental delay after normal infancy	May develop dystonia

Table 2.1. Continued.

Name	Primary defect	Typical course	Significance for surgical management
Mannosidosis	Alpha-mannosidase deficiency	Several types, usually with cognitive limits and minimal progression	
Fucosidosis	Fucosidase deficiency	Progressive mental retardation	Develop significant spasticity
Galactosialidosis	Neuraminidase and beta-galactosidase deficiency	Develops progressive myoclonus and extrapyramidal signs	Thoracolumbar spinal deformity may be present
Salla disease	Sialic acid transport deficiency	Mental and motor retardation, progressive	Course varies
Aspartylglycoaminuria		Has mental deterioration in late childhood or adolescence	Causes bone deformities, mitral valve insufficiency
Pompe's disease		Hypotonia	Severe mental retardation Early death
Batten disease (infantile form)	Neuronal ceroid-lipofuscinosis	Severe brain atrophy	Anxiety and autistic behavior Death after a prolonged vegetative state Has repetitive hand movements that may be confused with Rett syndrome
Spielmeyer–Vogt–Sjogren (juvenile form)		Condition starts in middle childhood	Slower course Death in 15–30 years
Kufs' disease (adult form)		Present with behavioral changes and dementia	
Amino acid metabolism	Many causes, only those more relevant included		
Phenylketonuria (PKU)	A defect in the hydroxylation of phenylalanine to tyrosine; the defect may occur in one of two enzymes or two required cofactors	Untreated children develop severe mental retardation and self-abuse	With early dietary treatment most of the symptoms can be avoided Requires treatment until age 4–8 years
Hyperphenylalaninemia (HPA)	Same as PKU		
Maple syrup urine disease	Organic aciduria; many subtypes	Disease varies from rapid progression to later onset or minimal progression	May cause acute coma Treatment varies by the specific defect Most of these conditions cause most of the problems during periods of stress when the body may depend on protein metabolism for energy source; this is especially true during major surgical procedures and can usually be avoided by using high-glucose infusion such as a 10% glucose solution intra- and postoperatively Blood pH level needs to be monitored and urine should be monitored for ketosis If proper precautions are not taken, ketoacidosis, hyperammonemia, and hyperlacticemia may develop and cause cerebral edema with further neurologic injury
Glutaric aciduria	Glutaryl-CoA dehydrogenase deficiency	Several types	Untreated neurologic effects leave the child with severe dystonia Cognitive process more preserved Stress causes a ketoacidosis, which causes brain injury Neurologic effects can be avoided with early dietary treatment Must take all the same precautions as noted for maple syrup urine disease

(*continued*)

Table 2.1. Continued.

Name	Primary defect	Typical course	Significance for surgical management
Homocystinuria	Cystathionine beta-synthase deficiency	Cause mental retardation and spasticity	Develop dislocated lens Also have thromboembolic disorder May present with a Charlie Chaplin-like walk Other common bone deformities include pectus, genu valgum, biconcave vertebra, epimetaphyseal widening Because of the thromboembolic problems, even children should probably have anticoagulation during surgical procedures
Sulfite oxidase deficiency		During infancy children have poor feeding, severe seizures, and present with quadriplegic pattern motor involvement Usually die in early childhood	
Tyrosinemia		Present with liver failure and neuropathy	Also often complain of severe leg pain Course is variable
Tetrahydrobiopterin deficiencies ("malignant HPA")	Same pathway as PKU and HPA	Children have progressive deterioration even with appropriate dietary treatment Children have progressive spasticity and limb rigidity Sometimes with dystonia or athetosis	Clinical course is variable
Nonketotic hyperglycinemia	Glycine accumulates because it cannot be metabolized	Course is usually with severe seizures and short-term survival, although some develop a more typical spastic CP pattern	
4-Hydroxybutyric aciduria	GABA neurotransmitter metabolism error	Presents with a static hypotonia and ataxia	
Urea cycle disorders	Ammonia accumulation causes brain injury	There are a number of different deficiencies, all with a similar presentation, but with varying severity	These conditions are like maple syrup urine disease in that during stress periods, such as acute sepsis or major surgical procedures, patients must be protected from high protein metabolism, which will cause the ammonia level to raise, running the risk of developing cerebral edema; this can be prevented with high-glucose fluid infusion, usually using 10% dextrose
Citrullinemia			Hepatomegly common
Argininosuccinic aciduria			Often have brittle hair Hepatomegly common
Arginase deficiency			Usually presents as a quadriplegic pattern CP with progressive spasticity
Vitamin metabolism disorders	Many are autosomal dominant inherited		
Multiple carboxylase deficiency	Impairment of the biotin recycling pathway	Skin rash, hypotonia, seizures, ataxia	Symptoms improve with high-dose biotin treatment
Vitamin B_{12} metabolism defect		Anemia, seizures, mirocephaly, pancytopenia, malabsorption Variable presentation	
Folate metabolism defect		Similar to B_{12} deficiency	

Table 2.1. Continued.

Name	Primary defect	Typical course	Significance for surgical management
Lactic acidosis (respiratory chain disorders)	Defect in the terminal step of the energy production cycle		The workup and diagnosis of many of these conditions require a skeletal muscle biopsy because the muscle is often involved This biopsy is also how to study mitochondrial function
Mitochondrial cytopathy		Usually presents in early infancy or early childhood with delayed motor skills, fatigue, muscle pains	The response is variable, from long static period to spontaneous improvement to sudden deterioration
Multisystem disorders			
Kearns–Sayre syndrome		Normal at birth	Develop headaches, mental retardation, peripheral neuropathy
Mitochondrial myopathy	Ragged red muscle fibers	Often present with stroke-like symptoms between childhood and young adulthood	High incidence of heart block and, if surgery is planned, the team needs to be prepared to insert a cardiac pacemaker
Alpers syndrome	Many different defects are probably causing this clinical syndrome	Autosomal recessive condition of progressive spastic quadriplegic pattern CP syndrome	
Leigh syndrome	Syndrome defined by necrotizing encephalomyelopathy Probably has multiple molecular causes	Course is extremely variable but usually progressive, although there may be long static periods	
Lactic acidosis			
Pyruvate dehydrogenase deficiency	Defect of pyruvate entry to mitochondria	Presents with highly variable hypotonia, seizures, failure to thrive	Some die in early childhood and others survive long term with a severe quadriplegic CP pattern
Mitochondrial fatty acid defects		Very variable with muscle weakness, cardiomyopathy, seizures	
Carnitine deficiency	Because of inability to metabolize protein, depends on glucose for energy	Presents in childhood with muscle weakness and cardiomyopathy	Under stress, such as major surgery, must give high-glucose infusion or there will be no energy even for the heart to function
Peroxisomal disorders	All have autosomal recessive inheritance		
Zellweger syndrome		Hypotonia	Poor swallowing Failure to thrive Develop severe equinovarus feet and flexion contractures Stippled calcification in the bones, especially the patella
Adrenoleukodystrophy		Same as Zellweger but milder form	
Refsum's disease		Similar but is the mildest form	
X-linked adrenoleukodystrophy		Variable, but males are always more affected than females	
Rhizomelic chondrodysplasia punctata		Rhizomelic dwarf with joint contractures	Calcification in the epiphysis and soft tissues Also with mental retardation
Wilson disease	Disorder of copper metabolism	Early on have facial masking, then develop tremor	Later develop a Parkinson-like presentation with psychiatric problems Have hepatic dysfunction When giving medication, must consider liver function
Lesch–Nyhan syndrome	X-linked	Very variable course and usually presents with hypotonia, torsional dystonia, mental retardation, self-abuse	Develop gouty arthritis
Enzyme defect allowing			

seriously disabling. Alternately, many disorders of intermedullary metabolism have acute insults during toxic events before the diagnosis has been made. With proper management, these disorders become static and mimic similar children with CP.

These metabolic disorders often require very specific management protocols during surgery. An example of such a condition is glutaric aciduria type 1, which presents with infants who are normal. When an infant experiences a stress, such as a childhood illness with a high fever, an acidosis develops that causes damage to the brain, especially the putamen and caudate areas. This insult leaves the child with a wide range of spastic and movement disorders, often with significant dystonia.[17] This neurologic disorder is static if the proper dietary management is carried out; therefore, the orthopaedist can approach this child similarly to a child with CP. However, these children must be prevented from becoming acidotic during operative procedures by infusing high levels of glucose, usually using a 10% dextrose solution as the intravenous fluid.

A wide variety of infections leave children with permanent neurologic deficits. Most of these deficits are static and therefore definitely fall into the CP diagnosis group. Prenatal and neonatal viral infections are the most common infectious cause of CP. Cytomegalovirus (CMV) leaves 90% of children with mental retardation and deafness, but only 50% develop CP or motor defects. Children who develop congenital rubella infections very commonly will have mental retardation; however, only 15% develop CP.[1] Neonatal herpes simplex infection has a high mortality rate, and 30% to 60% of survivors have some neurologic sequelae, although CP is not common. In utero varicella zoster infection causes high rates of CP. This same high rate is seen in lymphacytic choriomeningitis, which is a rodent-borne arenavirus. All these conditions cause neurologic insults that are static and should be treated as CP. Infections with human immunodeficiency virus (HIV) may cause neurologic sequelae; however, this is a progressive encephalopathy and these children should be treated anticipating a very short life expectancy. The most common parasite is *Toxoplasma gondii,* which is an intracellular parasite whose most common host is the household cat. With aggressive medical treatment, the infection can be eradicated, and approximately 30% of children are left with CP and mental retardation. Neonatal bacterial meningitis may be caused by many organisms and may be very severe, with as many as 30% to 50% of survivors having CP.[1] In our experience, most of these children who survive bacterial meningitis and have CP will have very severe spastic quadriplegic pattern involvement.

Temporary neurologic deficits are caused by many toxic agents, with alcohol being the most commonly encountered. Alcohol almost never causes a static neurologic deficit. Also, children with prolonged anoxic events, such as near drowning, near hanging, or near asphyxia, can make remarkable recoveries. However, when these children do not recover completely, they are usually left with extremely severe neurologic deficits and are among the most neurologically disabled individuals in our practice. These children tend to be relatively healthy and, in spite of severe neurologic deficits, tend to grow and thrive physically with good nursing care. One child in our practice has been ventilator dependent for 10 years from an anoxic event at age 9 months.

As noted in the beginning of this chapter, knowing the exact etiology is not always important to care for children's motor disabilities; however, it is important to understand whether these lesions are static or not. Also, parents may be more relaxed if physicians have some understanding of the specific etiology, if known, of their children's problems.

Epidemiology

Because of the wide variety of causes of CP, the exact numbers from different studies do not completely agree. However, there is remarkable similarity in the prevalence across the world, from Sweden in the 1980s with a prevalence of 2.4 per 1000[18] and 2.5 per 1000 in the early 1990s,[19] 2.3 per 1000 from Atlanta,[11] and 1.6 per 1000 in China.[20] Considering the difficulty in making specific diagnoses, and especially finding mild cases, these numbers probably reflect much more variation in counting than clear differences in prevalence. A report from England, which is representative of many studies, shows that there has not been much change in prevalence over the past 40 years. However, the patterns of CP have shifted more toward diplegia and spastic quadriplegia and away from hemiplegia and athetosis.[21] This change probably reflects increased medical care with better obstetric care and some increased incidence from survivors of neonatal intensive care units. Also, multiple births have increased with increasing maternal age,[22] and these multiple births have a substantially higher risk of developing CP. The reported prevalence rate per pregnancy for singles is 0.2%, for twins 1.5%, for triplets 8.0%, and for quadruplets 43%.[23]

Terminology and Classification

Although understanding the specific etiology of CP is not very helpful for physicians treating motor problems, by segmenting this very diverse condition by cause, patterns that are useful in planning treatment can be identified. There are many ways of classifying CP, one of which is by etiology. However, for the treatment of motor disabilities it is much more important to classify children by anatomic pattern and specific neuromotor impairments than by the cause of the CP. Classifying CP in this way provides a framework in which to discuss the functional problems of individuals in their whole environment.

A framework for understanding individuals with limited motor function has been agreed to at an international forum held in 1980, organized by the World Health Organization (WHO). The report is entitled "Classification of Impairments, Disabilities and Handicaps."[24] In this report, the term "impairment" defines the primary lesion and pathology, such as the problem with the brain that caused the spasticity, and includes the direct effects of the spasticity, such as the dislocated hip caused by the spastic muscles. "Disability" is used to mean the loss of function that individuals experience because of the impairment; therefore, the inability to walk or sit well is a disability arising from the impairment. The "handicap" is the result of limits in the environment and society, which limit individuals as a result of their specific disability. Therefore, an individual who uses a wheelchair has a handicap if he wants to visit a friend and the only way into the house is up a long flight of stairs. This inability to socialize is the handicap and, for many adults, is what impedes them from being integrated into full society of jobs, friends, and social entertainment.

In 1993, the National Center for Medical Rehabilitation Research (NCMRR) added to the WHO classification by dividing impairments into "pathophysiology" and "impairment." In this classification, "pathophysiology" refers to the primary problem, such as the brain lesion, and "impairment" refers to the secondary effects, such as spasticity and the dislocated hip. "Functional impairment" was added to reflect the inability to do activities

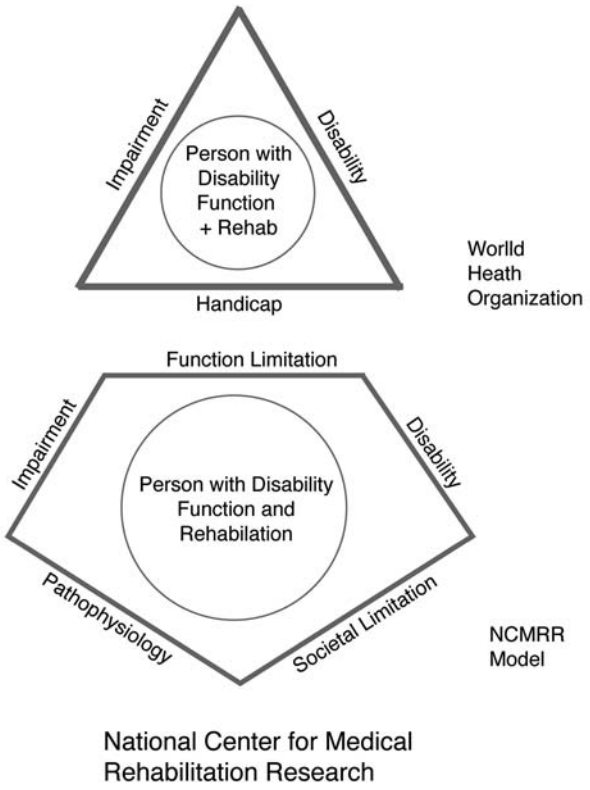


Figure 2.5. The WHO initially developed a model for disability that was later expanded by the USA National Center for Medical Rehabilitation Research. The concepts of both models are similar, with a focus that expands the understanding that problems of function are related beyond the isolated anatomic problem of an individual person.

such as walking that is a direct result of the impairment. "Disability" has retained almost its original meaning, and "handicap" has been renamed "societal limitations" to clarify where the problem of the limitation arises.[25] Although there are some merits to the changes NCMRR made to the WHO report for research purposes, the complexity does not work well in thought of daily practice; therefore, in the remainder of this text, the WHO definitions and terminology are used (Figure 2.5).

Anatomic Classification

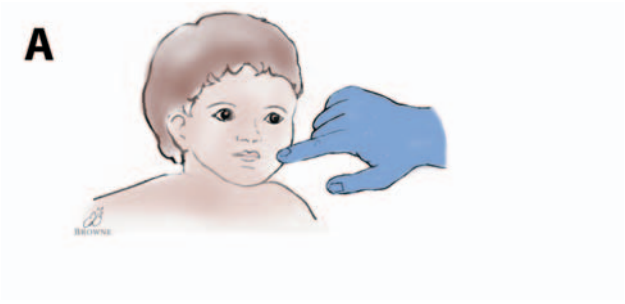
The most useful primary classification for children with CP is based on the anatomic pattern of involvement. This involvement is the first classification used by physicians treating motor impairments, as it gives a very general sense of severity and a general overview of what patients' problems likely are. Classification into hemiplegia, which involves one half of the body; diplegia, which involves primarily the lower extremities with mild upper extremity involvement; and quadriplegia, which involves all four limbs, is most useful. In general, individuals with hemiplegia and diplegia can walk, and those with quadriplegia use wheelchairs as their primary mobility device. For patients who do not clearly fit these patterns, many other names have been suggested. Double hemiplegia has been suggested for children with upper and lower extremity involvement that is much more severe on one side than the other. Triplegia has been suggested for individuals who have a hemiplegic pattern on one side and a diplegic pattern in the lower extremities. There are rare children who appear to have hemiplegia and diplegia, which would make anatomic sense, so this term triplegia has some merit; however, it does not aid in treatment planning.

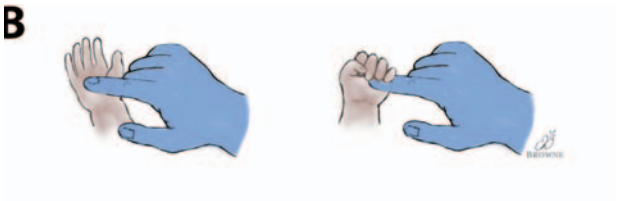
Monoplegia is used when one limb is primarily involved; however, from a motor treatment perspective, these children are treated as if they had mild hemiplegia. In North America, the term paraplegia implies a pure lower extremity paralysis and is used only for spinal cord paralysis because almost all children with brain origin disability will also have some upper extremity involvement, although it may be very minor. Pentiplegia is occasionally used to define the most severely impaired individuals who have no independent head control. This term adds little over the use of quadriplegia in planning motor impairment treatment; therefore, it has not gained widespread use.

Evolutionary Pathology

Even though there are many causes of CP, there are few recurring anatomic patterns of involvement because damage to specific areas, regardless of how the damage occurs, creates similar patterns of impairment. However, a specific region of brain injury can cause variation in the impairments because the initial injury also overlies normal development, which continues after the injury. Because all these injuries occur in the young and immature brain, growth and development over time affects the impairment. A brain injury occurring in early pregnancy, meaning most congenital syndromes, has a different presentation than an injury occurring in a 4-year-old child.

The first aspect of this pathology is to understand the presence of very early primitive reflexes that should disappear as normal children grow. The cutaneous reflexes, mainly finger and toe grasp, occur with stroking of the skin on the palm or on the sole. The sucking and rooting reflexes are similarly initiated with stroking of the face and lips (Figure 2.6). The labyrinthine reflex is a response to the inner ear being stimulated by changing a child's position (Figure 2.7). When held prone, a child will flex, and when placed supine, a child will extend. The proprioceptive reflexes are initiated by stimulating the stretch receptors in the muscles and the position sensors in the joints. This reflex creates the asymmetric tonic neck reflex (ATNR) such that when the head is turned to one side, the leg and arm on that side extend (Figure 2.8). The symmetric tonic neck reflex (STNR) causes the arms to flex and





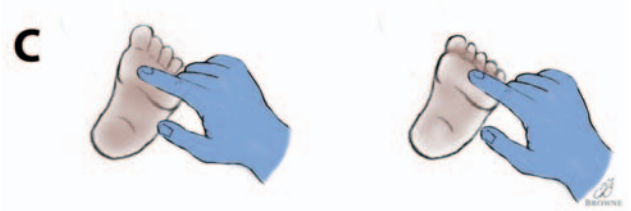


Figure 2.6. The most primitive reflex is the sucking reflex, which is stimulated by contact of the infant's perioral area (A). The hand (B) and toe grip (C) grasp reflexes are also present at birth and are stimulated by stroking the palm or plantar surfaces. Babies' early lives are dependent on the sucking reflex and, before high-level medical care, babies who lacked the sucking reflex always died.

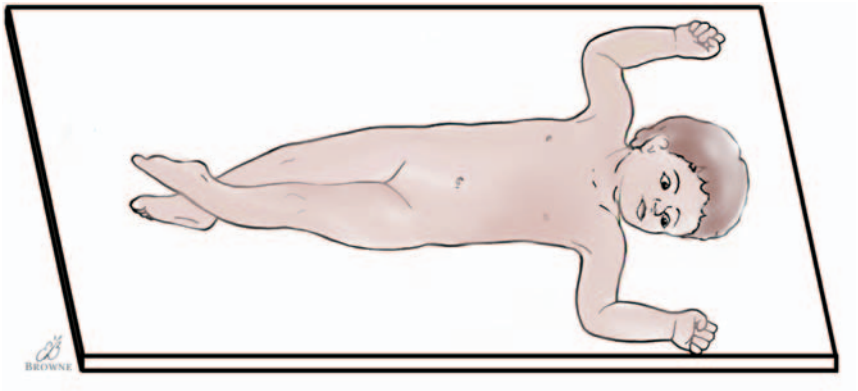


Figure 2.7. The tonic labyrinth reflex shows the baby with abducted shoulders, flexed elbows, adducted extended hips, and extended knees and ankles. This posture primarily occurs with the baby in the supine position.

Figure 2.8. The asymmetric tonic neck reflex is activated by turning the child's head. The side to which the face turns causes the shoulder to abduct with elbow and hand extension. The leg on the same side also develops full extension. On the opposite side, the shoulder is also abducted but the elbow and hand are fully flexed and the leg is flexed at the hip, knee, and ankle. By turning the head to the opposite side, the pattern reverses.

the legs to extend when the neck is flexed, and the opposite happens when the neck is extended. Both the ATNR and the STNR are suppressed by age 6 months.[26] The moro reflex is a sudden abduction and extension of the upper extremity with finger extension when a child is lifted, followed by shoulder adduction, elbow flexion, and closing of the hand as the child becomes comfortable again (Figure 2.9). Usually, this reflex is absent by 6 months of age. The parachute reflex occurs when a child is held upside down and lowered toward the floor. If the response is positive, which should occur by age 12 months,[26] the child should extend the arms in anticipation of landing on the hands (Figure 2.10). The step reflex, also known as foot placement response, occurs when the dorsum of the foot is stimulated; the child will flex the hip and knee and dorsiflex the foot in a stepping response. Usually, this reflex is suppressed by age 3 years (Figure 2.11). It is important to separate this reflex stepping, which some parents occasionally discover, from volun-

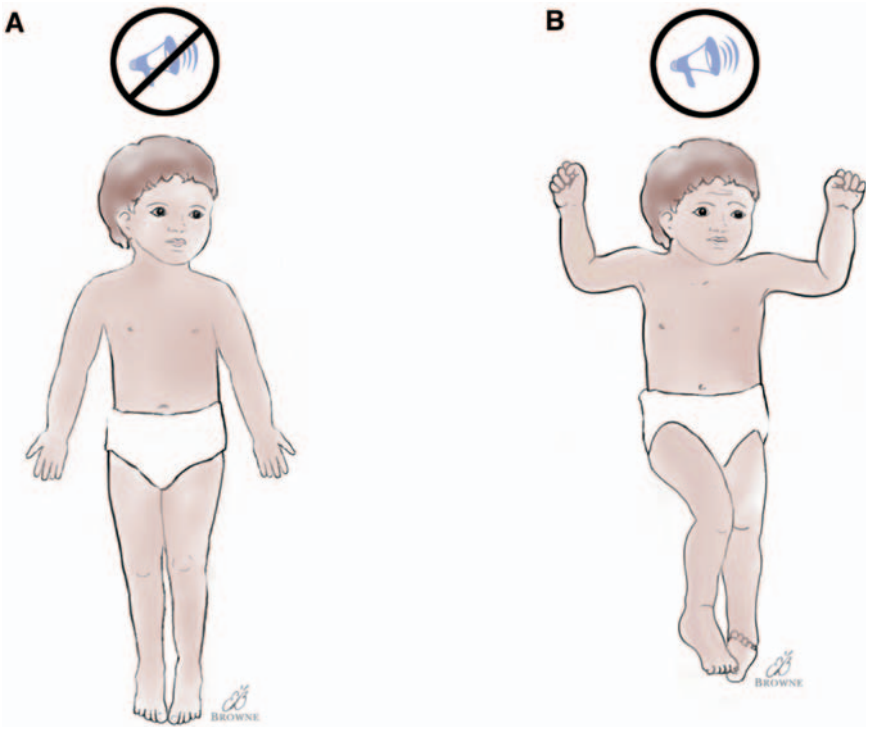


Figure 2.9. The Moro reflex is initiated with a loud noise, such as a hand clap, that causes the child to have full extension of the head, neck, and back. The shoulders abduct and the elbows extend. The legs also have full extension. After a short time, the pattern reverses and the head, neck, and spine flex; the arms are brought to the midline; and the legs flex.

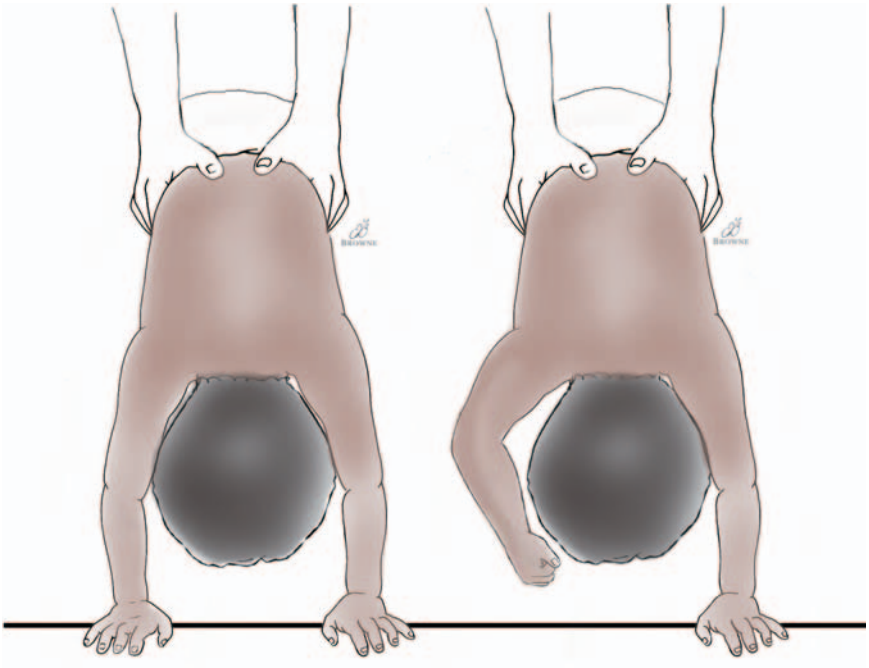


Figure 2.10. The parachute reaction is initiated by holding the child at the pelvis and tipping him head down. As the child is lowered toward the floor, he should extend the arms as if he were going to catch himself with his arms. This self-protection response should be present by 11 months of age. If the child has hemiplegia he will often only reach out with the extremity that is not affected. The affected extremity may remain flexed, or will extend at the shoulder and elbow but with the hand kept fisted.

tary step initiation. So long as a child's only stepping is the step reflex, the prognosis for achieving full gait is limited.

Although the presence of these reflexes after they should have disappeared is a negative neurologic sign, we have not found them helpful in making a specific prognosis as outlined by Bleck, who reported that the presence

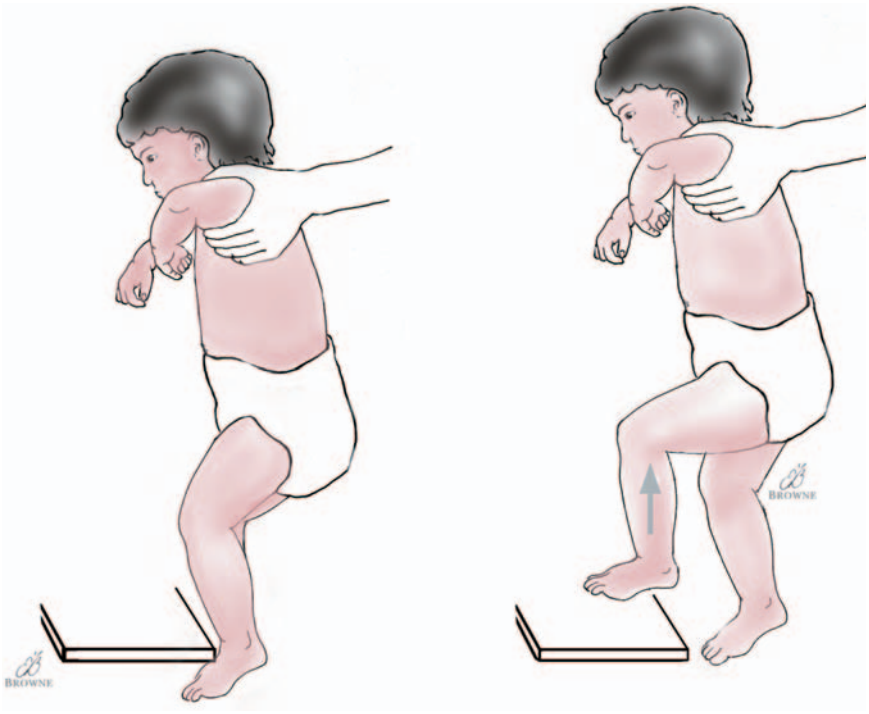


Figure 2.11. The foot placement reaction or step reflex is initiated with the child held under the arms or by the chest. When the dorsum of the foot is stimulated at the edge of a table, the child will flex the hip and knee, simulating a stepping action.

of two or more abnormal reflexes at age 7 years means a child has a poor prognosis to walk 15 meters independently. If one abnormal reflex is present, prognosis is considered guarded, and if no abnormal reflexes are present by age 7 years, the prognosis for walking is good.[26] Clearly, the absence of a parachute reflex at 18 months of age with persistent ATNR is not a good combination; however, it is not an absolute bad prognosis either. The presence of significant hyperextension reflex response, demonstrating opisthotonos, is a bad prognosis for functional gain because learning control to overcome this extensor posturing is very difficult. Instead of using these rather poorly defined abnormal reflexes at age 7 years, we have found that children who are walking at age 7 should continue to walk equally as well after completion of growth; therefore, if one desires to know how well a child will walk, look at the child walking, not his abnormal reflexes. Only a minimal improvement in ambulatory ability can be expected after age 7 years in children who have had appropriate therapy and orthopaedic corrections and have the musculoskeletal system reasonably well aligned. There are exceptions to the rule that gait function has plateaued by age 7 to 8 years, and these are usually seen in children with severe cognitive deficits. The most significant exception to this rule we have seen is a 12-year-old child with severe mental retardation who refused to weight bear before age 12, then started independent ambulation at age 12.5 years.

Deviation from Normal Development

As children mature from infancy to adolescence, there are many factors occurring in tandem, all of which come together in full-sized and normal motor functioning adults. To help develop a treatment plan for children with CP, it is important to have a concept of normal development. All innate normal motor function, such as sitting, walking, jumping, running, reaching, and speaking, is a complex combination of individual motor skills that allow development of these activities of daily living. Other activities, such as playing a piano, dancing, gymnastics, and driving a car, require much more learning and practice to remain proficient. These motor activities all include volitional motor control, motor planning, balance and coordination, muscle tone, and sensory feedback of the motion.

As babies mature from infancy to 1 year of age, neurologic maturity develops rapidly from proximal to distal. To demonstrate, children first gain head control, then develop the ability to weight bear on the arms, followed by trunk control and the ability to sit, then develop the ability to stand (Table 2.2). This progressive distal migration of maturation includes all the parameters of the motor skills. An early sign of abnormalities may be the use of only one arm for weight bearing, different tone in one arm, or a different amount of muscle tone between the arms and the legs. Children who move everything randomly, but are not doing volitional movements at the age-appropriate time, may be cognitively delayed. Children who show an early preference for one side or mainly use one side will probably develop hemiplegic pattern CP. Children who do not develop distal control for standing or sitting will probably develop quadriplegic pattern CP. These deviations in normal developmental milestones are usually the first signs of neurologic problems. Each individual child has their own rate of development; therefore, when contemplating the diagnosis of CP, it is important to consider the upper range of normal instead of the mean, which is quoted in most pediatric books (see Table 2.2).

Table 2.2. Normal developmental milestones.

Gross motor skill	Mean age of development	Abnormal if not present by:
Lifts head when prone	1 month	3 months
Supports chest in prone position	3 months	4 months
Rolls prone to supine	4 months	6 months
Sits independently when placed	6 months	9 months
Pulls to stand, cruises	9 months	12 months
Walks independently	12 months	18 months
Walks up stair steps	18 months	24 months
Kicks a ball	24 months	30 months
Jumps with both feet off the floor	30 months	36 months
Hops on one foot with holding on	36 months	42 months

Source: Adapted in part from *Standards in Pediatric Orthopedics* by R.N. Hensinger.[27]

Patterns of CP can be categorized further by using the elements of motor function required for normal motor task execution. This categorization has direct implications for treatment. All mature motor activities should be under volitional control with a few exceptions of basic responses, such as the fright response or withdrawal from noxious stimuli (e.g., burning a finger). Motor activities that are not completely under volitional control are termed "movement disorders" and can be separated into tremor, chorea, athetosis, dystonia, and ballismus. Tremor, a rhythmic movement of small magnitudes that usually involves smaller joints, is not a common feature in children with CP. Chorea involves jerky movements, most commonly including the digits, and has varying degrees of magnitude of the range of motion. Athetosis is large motions of the more proximal joints, often with an extensor pattern predominating. Fanning and extension of the digits is included as a part of the proximal movement. Each patient has a relatively consistent pattern of athetosis. Dystonia is a slow motion with a torsional element, which may be localized to one limb or involve the whole body. Over time, the motions vary greatly, and the pattern may completely reverse, such as going from full-extension external rotation in the upper extremity to full flexion and internal rotation. Dystonia can be confused with spasticity because, within a very short time period, if the changes are not seen, the dystonic limb looks very similar to a spastic contracted limb. Ballismus, the most rare movement disorder, involves random motion in large, fast patterns focused on the whole limb.

Motor control and planning of specific motor patterns requires a combination of learning to plan the motor task and then execute the functional motor task. This concept is best visualized in the context of a central motor program generator, which suggests that, like computer software, there is a program in the brain that allows walking. For the more basic motions such as walking, the central program generator is part of the innate neural structure, but for others, such as learning gymnastic exercises, it is a substantially learned pattern. Children who do not have function of this basic motor generator for gait cannot walk, and there is no way to teach or implant this innate ability. If there is some damage to the brain involving the central motor generator, gait patterns such as crouched gait more typically develop, which probably represents a more immature version of bipedal gait. These gait problems are discussed further in the chapter on treating problems of gait in children with CP (see Chapter 7).

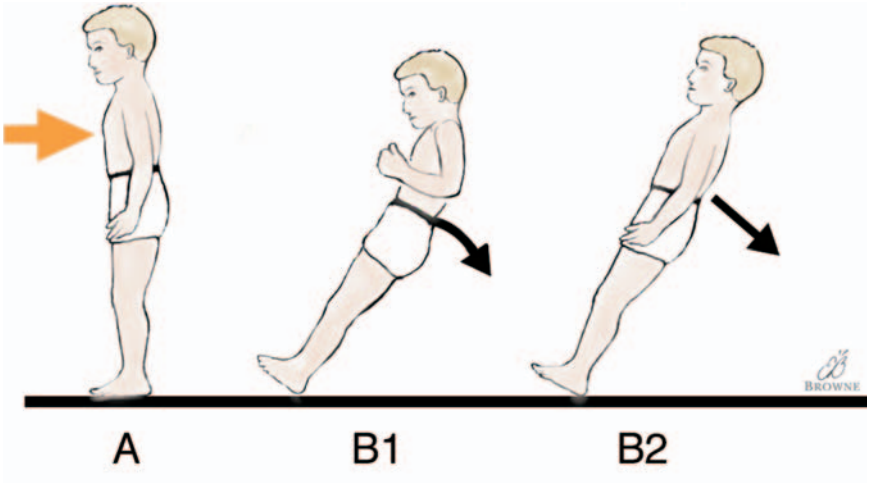


Figure 2.12. A normal child will demonstrate equilibrium reactions such that they will respond by extending the arms in the direction of the expected fall to catch themselves or by flexing forward into a ball if they are falling backward (B1). By an automatic reflex, the child will move the head in the opposite direction of the fall to prevent striking the head as the primary area of contact. A child lacking these equilibrium responses will fall over like a falling tree with no protective response when given a small push (B2). This is a very poor prognostic sign for independent ambulation, although some children can learn to control this response with appropriate therapy.

Balance, which means the ability to maintain one's position in space in a stable orientation, is required for normal motor functioning. A lack of balance causes children to overcompensate for a movement and be unable to stand in one place. Ataxia is the term used to mean abnormal balance. Also, feedback to the motion and position in space is important for maintaining motor function. In children with CP, sensory feedback may be considered part of the balance spectrum as well, but the problems that are usually considered in this spectrum do not typically come under the umbrella of ataxia. For example, when a child stands and starts to lean, the lean should be perceived and corrected. Children with ataxia often overrespond by having excessive movement in the opposite direction. Additionally, there are children who do not recognize that they are falling until they hit the floor, and as a consequence, they tend to fall like a cut tree (Figure 2.12). This pattern of sensory deficiency makes it extremely dangerous for affected children to be upright and working on walking because of the risk of sustaining an injury from a fall.

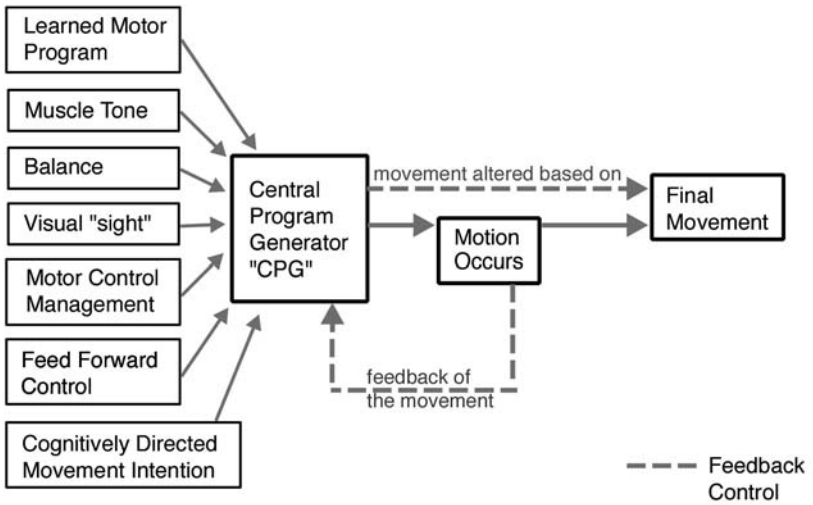


Figure 2.13. The control of human gait is very complex and poorly understood. There is some combination of feed-forward control, in which the brain uses sensory feedback and prior learning to control movement, with a closed-loop feedback system in which the brain responds by altering the control signal based on the sensory feedback of how the anticipated movement is progressing. Many movements probably use a combination of feed-forward control and feedback control.

Another important aspect of normal function is muscle tone. Muscles can respond appropriately only when they generate tension; therefore, their ability to function properly requires that this tension be carefully controlled. Based on increasing understanding of controller theory developed in the field of robotics research, the inherent stiffness that adds resistance to motion is important in developing fine motor control. Motor control is a very complex area involving learning and sensory feedback with several different patterns (Figure 2.13). Normal muscle tone is probably a key element of motor functioning. Abnormalities in motor tone are the most common motor abnormalities that occur in children with CP. Increased motor tone is called spasticity. A more complete, classic definition of spasticity is a velocity-dependent increase in resistance to motion or clasp-knife stiffness, such that the tension releases with a constant torque. Usually, hyperreflexia is part of this syndrome. The opposite end of spasticity is hypotonia, which means decreased muscle tension when the joint is moved.

Making the Diagnosis

There are no agreed-upon diagnostic criteria to make the diagnosis of CP in individual children. When a child is not meeting developmental milestones, has persistent primitive reflexes, or has significant abnormalities in the elements of motor function, a diagnosis of CP can be made. The history should clearly demonstrate that this is a nonprogressive lesion and is nonfamilial. If abnormalities in developmental milestones are marginal, the term developmental delay is the appropriate diagnosis. This diagnosis implies that these children will likely catch up with their normal peers. The diagnosis of developmental delay is not appropriate for a teenager who has mental retardation and cannot walk. Developmental delay typically does not refer to major abnormalities involving elements of motor function.

Making the diagnosis of CP in a very young child may be risky unless the child has severe and definitive disabilities. There is a well-recognized phenomenon of children occasionally outgrowing CP. For this reason, we prefer to make the diagnosis in young children only when it is clear and without doubt, but wait until at least age 2 years for children who have more mild and questionable signs. Making the diagnosis is important from families' perspectives so they know what is wrong with their children; however, making the diagnosis usually does not affect treatment.

Often, how much workup should be done before the diagnosis is made is questionable, with no definitive answer. In a premature child who has been following an expected course, no workup is indicated. If a child has hemiplegia with no recognized cause, but has a typical course, it is very unlikely that a magnetic resonance imaging (MRI) scan will show anything that will impact the child's treatment. The imaging study is obtained to rule out other treatable causes such as tumors or hydrocephalus, and the imaging studies are of very little use in making a prognosis or definitive diagnosis (Case 2.1). An aggressive workup of a child may be indicated when parents are interested in knowing the risk of recurrence in another baby. These children need a full neurologic workup, sometimes including skin and muscle biopsy, to rule out genetic diseases. A referral to a knowledgeable geneticist is recommended because there is some increased risk of a second child also having neurologic problems, even if no definitive diagnosis can be made. This increased risk is probably related to an as yet undiagnosed chromosomal anomaly that causes the CP in many children.

Case 2.1 Medical Imaging

The difficulty in making predictions extends to medical imaging, such as MRI or CT scans, during childhood. In a population, statistically more severe structural changes mean more severe motor and cognitive neurologic disability, as demonstrated by this MRI of Shawn, a boy with severe mental retardation and spastic quadriplegic CP (Figure C2.1.1). Other individuals may have equal cognitive and motor severity with a near normal MRI (Figure C2.1.2). There are also many individuals with severe structural changes on the MRI who are similar to Lauren, who is cognitively normal and has a triplegic pattern CP but ambulates using a walker (Figure C2.1.3). These cases demonstrate how important it is for physicians caring for children not to develop prejudices concerning an individual child's function based on imaging studies.

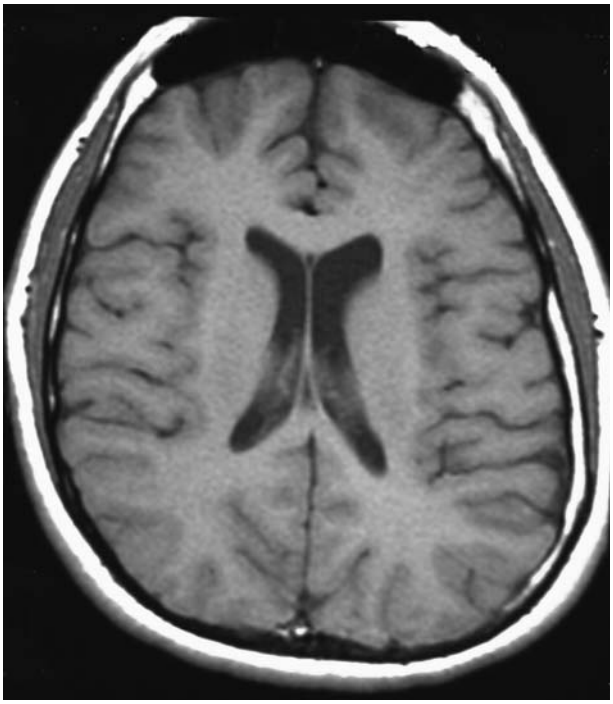
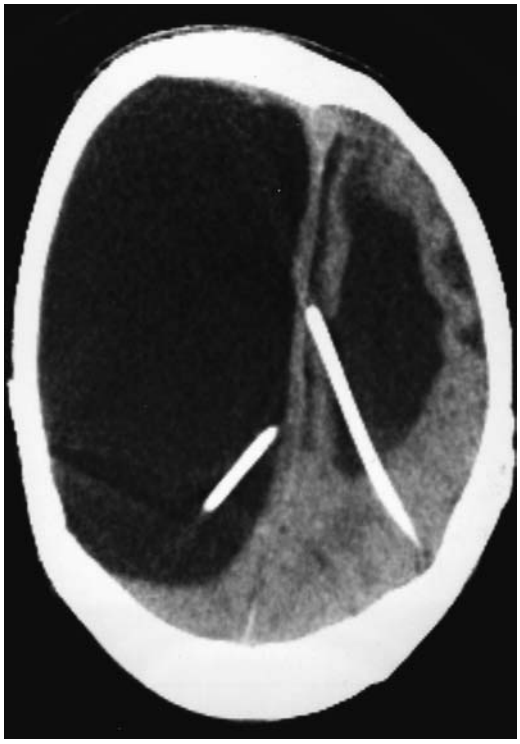


Figure C2.1.2



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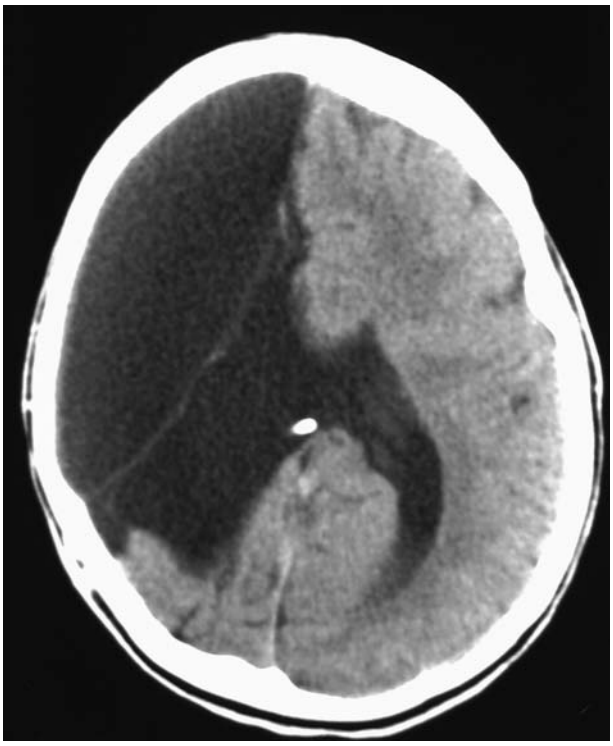

Figure C2.1.3

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