Cerebral palsy: causes, pathways, and the role of genetic variants

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Cerebral palsy (CP) is heterogeneous with different clinical types, comorbidities, brain imaging patterns, causes, and now also heterogeneous underlying genetic variants. Few are solely due to severe hypoxia or ischemia at birth. This common myth has held back research in causation. The cost of litigation has devastating effects on maternity services with unnecessarily high cesarean delivery rates and subsequent maternal morbidity and mortality. CP rates have remained the same for 50 years despite a 6-fold increase in cesarean birth. Epidemiological studies have shown that the origins of most CP are prior to labor. Increased risk is associated with preterm delivery, congenital malformations, intrauterine infection, fetal growth restriction, multiple pregnancy, and placental abnormalities. Hypoxia at birth may be primary or secondary to preexisting pathology and international criteria help to separate the few cases of CP due to acute intrapartum hypoxia. Until recently, 1-2% of CP (mostly familial) had been linked to causative mutations. Recent genetic studies of sporadic CP cases using new-generation exome sequencing show that 14% of cases have likely causative single-gene mutations and up to 31% have clinically relevant copy number variations. The genetic variants are heterogeneous and require function investigations to prove causation. Whole genome sequencing, fine scale copy number variant investigations, and gene expression studies may extend the percentage of cases with a genetic pathway. Clinical risk factors could act as triggers for CP where there is genetic susceptibility. These new findings should refocus research about the causes of these complex and varied neurodevelopmental disorders.

Key words: causes, cerebral palsy, DNA variants, epidemiological risk factors, genetic variants, genomics, heterogeneity, whole exome sequencing

Two international expert task forces addressed cerebral palsy (CP) causation in 1999[1] and 2003.[2] In 2014, the American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics, with many international consultants, updated these reports but chose to focus on neonatal encephalopathy and a variety of neurological outcomes rather than discuss CP causation specifically and did not directly address the ramifications of litigation following a diagnosis of CP.[3] Recent findings published after the 2014 report have identified likely causative genetic variants associated with CP cases and this review contributes to updating clinicians.

CP is a heterogeneous condition with multiple causes; multiple clinical types; multiple patterns of neuropathology on brain imaging; multiple associated developmental pathologies, such as intellectual disability, autism, epilepsy, and visual impairment; and more recently multiple rare pathogenic genetic variations (mutations). CP would be better named "the cerebral palsies" given that within the CP clinical spectrum there are many causal pathways and many types and degrees of disability. These various pathways and etiologies have each resulted in a nonspecific nonprogressive disorder of posture and movement control. Thus, CP should be considered as a descriptive term for affected individuals, with each case receiving adequate consideration of an underlying etiology. There has been little change in the prevalence of this diagnosis throughout the world, where population data are available.[1] It remains around 2-2.5/1000 births. Although there have been small statistical fluctuations in the CP rates among children born preterm, the rates of CP at term remain stable.[4] New interventions such as head or body cooling in selected

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cases with acute hypoxia have yet to significantly lower overall rates. Only a small percentage of cases are associated solely with acute intrapartum hypoxia.[5-8] Despite this, many cases are mislabeled as due to birth asphyxia.

Birth asphyxia

"Birth asphyxia" is an outdated term that may wrongly convey that a baby born with signs of fetal and neonatal compromise must have undergone an acute hypoxic event in late labor and/or birth. These clinical signs may also be present when there has been much longer-standing fetal compromise with possible secondary hypoxia near delivery.[1] Similarly, the term "hypoxic ischemic encephalopathy" has been replaced by the term "neonatal encephalopathy" as the large majority of newborn infants showing signs of encephalopathy does not have objective proof of acute hypoxia or ischemia at birth, but have other causes of perinatal compromise such as infectious or genetic.[9] Of note, only 13% of term babies who exhibit neonatal encephalopathy are later diagnosed with CP.[10]

At birth, nonspecific signs of fetal compromise such as meconium-stained amniotic fluid, nonreassuring fetal heart rate patterns, low Apgar scores, and neonatal encephalopathy could all be associated with either acute intrapartum timing or chronic long-standing timing of the pathologies (ie, beginning before labor and during pregnancy). The same signs can be caused by not only hypoxia and/or ischemia, but also by other factors such as infection, placental and umbilical vessel thrombosis, or an altered fetal inflammatory response.[1] Very recent studies suggest that many cases of CP are associated with genetic alterations (mutations) that may either directly cause CP or contribute to susceptibility to CP.[11,12] As yet, they are not detectable antenatally or preventable.

International consensus criteria to identify severe acute intrapartum hypoxia

There is now increasing evidence that babies given a "birth asphyxia" label due to clinical signs such as low Apgar scores often do not have primary asphyxia.[13,14] Many such babies are in ill health due to longer-standing problems. Acute or chronic hypoxia can cause a metabolic acidosis in the blood of the newborn and this has to be objectively measured in umbilical arterial blood gases at birth to ascertain if clinically severe hypoxia is contributing to the poor condition of the newborn. When metabolic acidosis is proven to be present, this is evidence of either acute hypoxia beginning in labor or chronic hypoxia (ie, long-standing compromise in pregnancy beginning before labor). Secondary asphyxia in labor is not necessarily the initial cause of the brain injury but may be a subsequent result of the established neuropathological process. International consensus criteria have been published and refined to help define cases where neuropathology may have become established only in labor and birth.[1,2] These 9 criteria have helped recognize the few cases of severe de novo acute intrapartum hypoxia (Table 1). These criteria, as a group, have been well verified.[15] The first 4 essential criteria have a high but not individually perfect correlation (94-100%) in acutely asphyxiated neonates. The 5 nonspecific timing criteria were individually less predictive, but were to be assessed together, and their consensus helps understand the likely timing of the neuropathology. In 2014, a third consensus statement similarly examined neonatal encephalopathy, rather than CP, and largely supported the criteria that define a

TABLE 1
International consensus criteria to determine a severe acute hypoxic event as a potential cause of cerebral palsy

Essential criteria to show presence of hypoxia at birth are:

1. A metabolic acidosis at birth (pH <7.00 and Base Excess <-12).
2. Early moderate to severe neonatal encephalopathy.
3. Cerebral palsy of spastic quadriplegic or dyskinetic type.
4. Exclusion of other identifiable causes of cerebral palsy, eg, coagulation or genetic disorders, infectious conditions, intrapartum pyrexia, antepartum hemorrhage, prematurity, intrauterine growth restriction, tight nuchal cord, complications of multiple pregnancy.

Five nonspecific criteria collectively point toward acute or chronic causes of hypoxia.
If most are met they suggest timing of neuropathology near delivery. If most are not met they suggest longer-standing pathological process. These criteria are:

5. Sentinel (signal) hypoxic event sufficient to cause sudden severe hypoxia in healthy fetus, eg, cord prolapse, antepartum hemorrhage, ruptured uterus.
6. Sudden sustained fetal heart rate bradycardia from that event.
7. Apgar score <4 after 5 min.
8. Signs of multisystem failure in neonate.
9. Early (within 5 d) neuroimaging signs of edema and intracranial hemorrhage.

In 2003, American College of Obstetricians and Gynecologists/American Academy of Pediatrics Cerebral Palsy Expert Task Force[2] updated 1999 criteria[1] on basis of published evidence to that date. Task force agreed with 1999 task force criteria and added fourth essential criterion was necessary, ie, that no major chronic cause of neuropathology should be present if intrapartum acute asphyxial cause was to be presumed. Also acute de novo intrapartum event severe enough to be associated with cerebral palsy would cause Apgar scores to remain at ≤ 3 after 5 min of birth. Lastly, it only accepted evidence of severe metabolic acidosis from arterial umbilical samples taken at birth, as blood gases can improve or worsen in first hour depending on successful or problematic neonatal resuscitation.

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