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REVIEW ARTICLE

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Cerebral Palsy

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Incidence

Cerebral palsy (CP) is the most common congenital neurologic disorder. The world wide prevalence of cerebral palsy is 2-2.5/1000 live births [1]. In the past it was thought to occur as a result of acute intrapartum hypoxic events. Recent epidemiological studies suggest that in only 10% of cases this is true, and 90% of cases are due to chronic events or congenital factors [2-4].

Definition and criteria

CP is a chronic disability of central nervous system origin characterized by aberrant movement and posture, appearing early in life and associated with defect or lesion of the immature brain.

Neonatal encephalopathy and hypoxic-ischemic encephalopathy (HIE) have been defined in term and near term infants as a group of criteria to collectively include altered consciousness, tone, reflexes, feeding ability respiration, and/or seizures, and may or may not result in permanent neurologic injuries. Previous epidemiologic studies show that only 19% of neonatal encephalopathy met old nonstringent criteria for neonatal intrapartum hypoxia. CP due to HIE must be preceded by neonatal encephalopathy. Incidence of CP due to intrapartum asphyxia is only 1.6/ 10,000 and 70% of neonatal encephalopathy occurs as a result of prenatal events. Additionally intense intrapartum monitoring in recent past has not reduced the incidence of CP. However, in the past, birth asphyxia due to poor obstetric management has been needlessly and without scientific basis implicated medicolegaly.

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Spastic quadriplegia, is the only type of CP associated with intrapartum acute hypoxic events. Dyskinetic or ataxic CP associated with learning problems, epilepsy, hyperactivity disorders, attention deficit or mental retardation do not have their origin in acute birth hypoxia.

History

Our current knowledge of cerebral palsy is highly enhanced by both internationally published scientific evidence and a joint project by the American College of Obstetricans and Gynecologists and the American Academy of Pediatrics (ACOG/AAP). A multidisciplinary International Cerebral Palsy Task force of scientists and clinicians published a consensus statement in 1999, which set out the criteria defining an acute intrapartum hypoxic event necessary to have had occurred prior to the onset of CP [5]. ACOG/AAP revised the international template and updated the literature on the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy in 2003 [6] (Table 1). Of the nine criteria four when present together help to prove the existence of severe hypoxia at birth. The remaining five when present collectively suggest intrapartal timing but are not specific to asphyxial insults. These efforts help to truly identify intrapartum hypoxic events and other pathologies responsible for CP. Recently, cord blood gases, placental pathologies and neonatal brain imaging allow better identification of antepartum etiologies. Additionally, definition of acute hypoxia and its correlation with neonatal nucleated red blood cells increase in chronic hypoxic events can be used to differentiate between acute and chronic pathologies [7-8].

Relationship between neonatal encephalopathy and cerebral palsys

Neonatal encephalopathy and HIE are related to CP and long term neurologic deficits specifically in term and near term infants in whom neurologic signs can be accurately recognized, classified, and scientifically studied.

Table 1. Criteria to define an acute intrapartum hypoxic event as sufficient to cause cerebral palsy.

A. Essential criteria (All four ncessary).

1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH<7 and base deficit > 12 mmol/L).
2. Early onset (within 24 hours) of severe or moderate neonatal encephalopathy in infants born at ≥ 34 weeks of gestation.
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type.
4. Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

B. Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, e.g. 0-48 hours, but are nonspecific to asphyxial insults.

1. A sentinel (signal) hypoxic event occurring immediately before or during labor.
2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal.
3. Apgar scores of 0-3 beyond 5 minutes.
4. Onset of multisystem involvement within 72 hours of birth.
5. Early imaging study showing evidence of acute nonfocal cerebral abnormality.

ACOG/AAP 2003 Template Criteria (Obstetric Gynecology, June 2006).

Table 2. Antepartum/Prenatal maternal medical, obstetrical and fetal characteristics that are statistically significant risk factors for newborn encephalopathy.

Risk factor	Risk	Risk OR (95% CI)
Maternal thyroid disease	No	1
	Yes	9.7 (1.97-47.91)
Preeclmpsia	No	1
	Yes	6.30 (2.25- 17.62)
Bleeding (moderate / severe)	No	1
	Yes	3.57 (1.30-9.85)
Viral infection	No	1
	Yes	2.97 (1.52-5.80)
Gestational age	39	1
	37	2.35 (1.11-4.97)
	38	1.18 (0.90-1.56)
	40	1.41 (1.17-1.70)
	41	3.34 (2.09-5.35)
	42	13.2 (5.03-34.83)
Centile birth weight	>90	1
	3rd - 9th	4.37 (1.43-13.38)
	<3rd	38.23(9.44-154.79)
Abnormal placenta	No	1
	Yes	2.07 (1.15-3.73)
Late/No prenatal care	No	1
	Yes	5.45 (0.47-62.98)

Adapted from Badawi et al BMJ 1998;317:1549-53 in Neonatal; Encephalopathy and Cerebral Palsy: Defining Pathogenesis and Pathophysiology ACOG/AAP, Jan 2003.

Very preterm and very low birth weight infants contribute disporportionately to occurrence of CP eg, 25% of the total number of CP cases come from those with a birth weight of < 1500g. These babies have stormy neontal course, respiratory and other vital problems. However they are hard to study since they do not exhibit typical neonatal encephalopathy pathophysiology and may have a variety of other neurologic deficits besides CP.

Maternal and fetal conditions as risk factors are depicted in Table 2.

Third trimester bleeding

Theoretically, vaginal bleeding and shock due to placenta previa and placental abruption can reduce placental perfusion and oxygenation of the fetus leading to neonatal encephalopathy resulting in CP. In reality, third trimester bleeding is rarely associated with HIE [9].

A prospective US study of 42,704 infants weighing > 2500 g from pregnancies complicated by bleeding due to placenta previa had a slightly higher risk of CP (OR of 6; 95% CI, 1,9-18.8)[10]. This risk was not elevated in those whose mothers had bleeding due to abruptio placenta although the risk of death in first year of life was greater for these infants.

A case control study of 46 normally weighing infants with spastic CP from California Birth Defects Monitoring Program revealed that neither placenta previa nor abruptio placenta were associated with increased risk of CP (OR 14.3 and OR 2.8 with 95% CI) [11].

In two case control studies from Western Austrialia involving babies > 2500 g, vaginal bleeding was associated with slightly increased risk of neonatal encephalopathy (OR 5.95%; CI 1.5-17.3 and OR 3.57; 95% CI 1.30 - 9.85) [12]. The second time the results were higher but not associated with hypertension.

Hence CP does not seem to be increased with vaginal bleeding due to placenta previa or abruption. Confounding variables of growth restriction, hypertension, coagulopathy, substance abuse etc, may be operative in genesis of HIE and its consequences.

Studies of CP in preterm infants are rare. However, in a Danish review, neither placenta previa nor placental abruption was found to be responsible for HIE or CP [13].

Underlying long standing and chronic conditions in third trimester vaginal bleeding may lead to fetal neurological injury antedating antepartum bleeding. Symptom of third trimester bleeding is rarely associated with HIE [14,15].

Inflammation, coagulation, infection and autoimmune diseases

Intrauterine infection is associated with CP in term and near term infants. It is now realized as the most common precursor of adverse neonatal outcomes viz., low apgars culminating in encephalopathy and CP.

Intrauterine infection may lead to hypotension, neonatal seizures, respiratory distress syndrome (RDS), preterm delivery and HIE. Intraventricular hemorrhage, periventricular leukomalasia, bronchopulmonary dysplasia and CP may result from these serious problems [9,16,17].

These and other responses imitate adult systemic inflammatory responses mediated by endothelial injury in adults. Over production of cytokines leads to brain damage in small infants. Chorioamnionitis increases periventricular leukomalasia in preterm infants. An increased risk of CP has been documented in preterm infants exposed to chorioamnionites (RR 1.9) [18]. Added exposure to asphyxia due to obstetric complications certainly makes this risk even greater.

Recent evidence suggests that intrauterine infection preceding pregnancy or arising early in pregnancy may persist from one pregnancy to next, and have significant impact on outcome [19].

Maternal and fetal response to intrauterine infection may be mediated by invidiual's genetically controlled inflammatory process [20]. Infectious and inflammatory processes may progress to all manifestations of intrauterine infections. Additionally altered immune recognition, cell damage and cell death from reactive oxygen species and damaging molecules may result from these responses. These mechanisms may persist causing cell damage even after the original processes are corrected [21,22].

Preterm and low birth weight

Intrauterine infection appears to be the most common cause of preterm birth in USA and possibly world over. Ascending infection from bacterial vaginosis from endogenous microflora, anerobes, mycoplasmas, gardenerella etc, or less often infection by way of maternal blood stream of microbes is often responsible for perinatal infection.

Elevated cytokine concentrations in amniotic fluid and cord blood have been associated with white matter damage and CP [21,23]. Severe neonatal morbidity due to neonatal sepsis including multiorgan involvement eg. pneumonia, respiratory distress syndrome (RDS), intraventricular hemorrhage and periventricular leukomalasia have been associated with increased levels of Il-6 in cord blood (78% vs 30%) [23].

Term infants

Ultrasound evidence of perivenricular leukomalasia and clinical markers of infection eg. chorioamnionitis, C-reactive proteins and recovery of causative microbes are closely associated [24]. Increased neonatal cytokines and evidence of neonatal thrombophilla are closely associated with CP [25,26].

Clinical and subclinical intrauterine infections are significant causes of reproductive loss and preterm birth. Infection and associated inflammatory cytokines are associated with increased risk of CP in all infants. Thrombophilia is associated with inflammatory activation in children manifesting CP and vice versa.

Chrioamnionitis

Interacting associations of intraamniotic infection, white matter lesions, echoluscency, and periventricular leukomalasia are under study. However, multiple studies demonstrate increased CP in chorioamnionitis in term and preterm infants [27-32].

Bacterial and viral causes of CP and neoneonatal encephalopathy

Bacterial perinatal infections including intrauterine infections are known to imitate adult systemic inflammatory responses involving cytokines, chemokines, coagulation factors, and

other cellular responses causing direct cell necrosis and inducing programed cell death.

A host of organisms have been observed in these infections, including group B streptococci, E. coli, klebsiella and proteus, hemophilus, listeria monocytogenes, salmonella etc.. Anerobes and mycoplasma may be recovered from amniotic fluid and often not cultured from the neonate [22-30].

Proteolytic enzymes released during killing of the microorganisms can perpetuate cell damage long after clinical infection has been controlled. Viral and protozoal perinatal infections are less common, involving < 5% of cases [16]. Organisms, causing brain damage due to viral/protozoal infections include, cytomegalovirus, herpes I and II, varicella-zoster, rubella and some enteroviruses. Toxoplasma and congenital malaria infections may be involved in causing brain lesions in the fetus occasionally.

Coagulopathies

Maternal and fetal coagulopathies and placental thrombosis are important contributors to fetal morbidity and mortality including stillbirth, early neonatal demise and organ thrombosis [31]. In addition to fetal coagulopathies, maternal coagulation abnormalities can be transmitted across placenta to the fetus.

Variety of brain injuries may occur prenatally and three major categories were seen during a review of nearly 100 autopsies [32]

1, Funisitis was associated with matrix/intraventricular hemorrhage.

2. Placental infarcts and chronic placental lesions were associated with white matter gliosis/necrosis.

3. Neuronal necrosis was linked to placental infarction/ abruption and vessel thrombosis.

Evidence of coagulopathies like factor V Leiden mutation, and protein C or protein S abnormalities without cytokines indicating absence of infection were seen in blood samples of 31 children with CP of unknown origin. All blood samples had cytokines indicating relationship between perinatal inflammation and coagulopathy [26].

Spastic CP in near term infants was associated with inflammation and coagulopathies. Both maternal and fetal thrombophilias eg. maternal antibodies to coagulation factors, cardiolipin in systemic lupus erythematosus and phospholipids, may injure early embryo and fetus causing fetal demise [33].

Fetal genome influencing outcome is well established in case of factor V Leiden mutation directly predisposing the fetus to thrombotic conditions and CP [34]. Other adverse outcomes in similar conditions may include intrauterine growth restriction, low birth weight, fetal distress, neonatal seizures, and a clinical picture resembling birth asphyxia. Cerebral infarction or intraventricular hemorrhage may be seen on imaging studies.

Coagulation disorder in mother (eg. antithrombin - III deficiency, abnormalities of protein C or S, and factor V Leiden mutation) may contribute to origin of CP. Only severe Maternal infections are associated with CP.

Epilepsy

Earlier data from the National Collaborative Perinatal Project Identified maternal mental retardation and seizure disorders as risk factors for CP which was not confirmed later [3,35]. Family history of neurologic disorders including seizure disorder is associated with a 2.5 fold increase in HIE in the infant. Antiepileptics are not a risk factor for CP. The link between maternal epilepsy or mental retardation and CP may only be an association.

Hypothyroidism

Maternal hypothyroidism is a risk factor for abnormal neurodevelopment in the child however it being causative in origin of CP needs further research and evidence.

Maternal severe hypothyroidism adversely affects fetal neurodevelopment and may be significantly linked to neonatal encephalopathy [36]. Transient hypothyroidism may be associated with abnormal neurodevelopment in preterm babies [37-39].

Alcohol, drugs, environmental factors

Maternal consumption of alcohol may result in neurologic, cognitive and behavioral abnormalities. However no relationship has been observed between maternal use of alcohol and CP [40,41]. Maternal use of cocaine and exposure to organic mercury may affect neurologic development and the latter has been linked to CP [42]. Environmental influence on etiology of CP has not been established to date. Association between CP and lead levels and maternal hyperthernia have not been fully investigated yet.

Antepartum events

Antepartum conditions associated with CP include preterm birth, intrauterine growth retardation and infections like chorioamnionitis, multiple pregnancies, coagulopathies congenital/genetic abnormalities etc.. All CP are not preceded

by HIE. These two conditions may have different timing and type of cerebral injury. Risk factors for neonatal encephalopathy are listed previously (Table 2). National Collaborative Perinatal Project collectively lists numerous antepartum conditions associated with CP [3,37]. None were present in more than 2% infants of normal weight. In infants of > 2500 g severe proteinuria, polyhydramnios, third trimester bleeding, and maternal seizures were significant indicators of CP. Multivariate analysis of this data failed to show statistical relationship. When a 5 minute apgar score was 0-3, the relationship of polyhydramnios, nuchal cord, and decreased fetal heart rate of < 100/minutes with CP was significant.

In a multivariate analysis, the strongest risk factor for neonatal encephalopathy was fetal growth restriction [9]. This risk increased with advancing gestational age beyond 38 weeks.

Multiple causal pathways lead to neonatal encephalopathy and CP. However, 70% of cases of neonatal encephalopathy were due to events present prior to onset of labor, and were not amenable to intervention by the provider.

Antepartum fetal monitoring and neonatal encephalopathy

The literature to demonstrate long term relationship between antepartum testing and neurologic outcome is scarce. Randomized prospective trials of antepartum testing have shown no benefit [43,44].

A single randomized trial of fetal movement counting has shown decrease in fetal death but no impact on neurologic outcome [45]. In an Australian study, a nonreactive positive contraction stress test was associated with 28% perinatal mortality and 27% neurologic deficit rate [46]. Manning et al [47] have shown incidence of CP to be 1.33/1000 in those infants who underwent biophysical profile vs 4.74/10000 among those who did not.

Overall predictive value of antepartum testing for prediction of long term neurologic abnormality is poor, though abnormal results are associated with more abnormal outcome. Antepartum electronic fetal heart rate monitoring has not shown to reduce CP. Antepartum fetal movement monitoring has shown to reduce fetal deaths.

Intrapartum monitoring and CP

Since 1970's, National Collaborative Perinatal Project data have concluded that routine auscultatory monitoring of FHR is not helpful.

Advent of electronic fetal monitoring is associated with fewer intrapartum and neonatal deaths, fewer low apgar scores, and less need for resuscitation. Randomized trials of electronic fetal heart rate monitoring vs intensive nursing and auscultations failed to show advantages of electronic monitoring seen in previous trials. In fact increased cesarean deliveries occurred [48-53]. The only benefit of electronic monitoring shown was decrease in neonatal seizures [54,55]. No benefit was observed in abnormal neurologic outcome. Opportunity for appropriate action to prevent bad outcome was still not available.

Use of scalp blood sampling for acid-base status with abnormal patterns decreased cesarean section rate [49]. Fetal pulse oxymetry for patients with nonreassuring tracings decreased cesarean delivery for abnormal tracings but increased cesarean deliveries for dystocia [56]. Further studies were recommended.

In an earlier study, intrapartum fetal monitoring analysis in 1,35,000 patients revealed fetal death rate to be 0.54/1000 in monitored group vs 1.76/1000 in nonmonitored group, with a death ratio of 3.26 favoring monitoring [57]. As previously stated, both intensive auscultation and electronic monitoring prevent fetal demise.

In a study by Nelson et al [58], fetal heart rate patterns associated with CP were repetitive late decelerations and decerased beat to beat variability. A high false positive rate of prediction was observed.

The National Institute of Child Health and Human Development consensus report has stated definition of reassuring fetal heart rate pattern to be extremely predictive of well oxygenated fetus. Reassuring pattern includes, normal baseline, moderate heart rate variability, presence of accelerations and absence of decelerations. It reiterated patterns indicative of impeding asphyxia and risk of neurologic injury associated patterns with recurrent late or severe variable decelerations or significant bradycardia and absent variability. A sentinel event precipitating these patterns is necessary when previously normal patterns become ominous. A fetus whose mother is admitted with abnormal pattern at the onset of labor may already have neurologic injury which cannot be improved by any means.

Specific fetal heart patterns indicate uteroplacental insufficiency and umbilical cord compression. Profound fetal hypoxia resulting in prolonged deceleration and leading to encephalopathy can occur due to any cause.

Intrapartum fetal monitoring has shown to reduce neonatal seizures. However, it is not associated with reduction in CP when compared with dedicated auscultation. It has high false positive rate of prediction for CP.

Acute catastrophic intrapartum asphyxia and neonatal neurologic injury : diagnosis to delivery time

Animal data have contributed profoundly to our knowledge of mechanisms of neurologic injury in the fetus. The pattern of neurologic insult following acute catastrophic hypoxic-ischemic insult usually involves the thalami and basal ganglia and is different from the pattern following chronic insult seen in the neonate involving cerebral cortex and the subcortical white matter predominantly [59,60]. The former is highly predictive of poor outcome and mimics animal studies of acute hypoxia. Additionally it may not be asscoiated with multiorgan system injury [60,61]. In an anlysis of 14 cases of isolated brain injury following acute asphyxia, the average duration of fetal heart decelertion was 32.1 minutes (range 19-51 minutes) [61]. A high metabolic rate of subcortical region may account for the damage to this region without involvement of other systems. Conversely, more chronic hypoxia associated with uteroplacental ischemia allows redistribution of blood supply and oxygen from the cerebral cortex and other organ systems to thalami and brainstem resulting in injury to the cortical region and multiorgan dysfunction.

Umbilical cord prolapse

Neurologic outcome and time needed for delivery in cord prolapse depend upon the presentation and station, and severity of uterine contractions (low vertex is associated with more severe outcome). Recent advents in neonatal management may have improved neurologic outcome due to better resuscitation. Fetal mortality and neurologic injury in cord prolapse are affected by the time from diagnosis to delivery, and the extent of the cord prolapse [62-65].

Shoulder dystocia

The pathophysiology in shoulder dystocia is similar to that in cord prolapse but more severe. Head to body delivery interval is the determining factor. In a review of 56 cases of shoulder dystocia, 47% had < 4 minutes and 20% had > 10 minutes head to body delivery interval. Twenty one babies had HIE. Autopsy on 18 of the 23 nonsurviving babies revealed acute hypoxic damage [66].

Uterine rupture

Perinatal mortality and morbidity associated with uterine rupture is dependent upon whether the fetus was extruded from the uterus or not. In a review of 106 cases, extreme neonatal morbidity including perinatal asphyxia was much worse when fetus was partially or completely extruded out of the uterus [67].

When delivery occurred within 17 minutes of onset of prolonged deceleration, no significant perinatal morbidity was seen. However, when prolonged fetal heart rate deceleration was preceded by 36-90 minues of severe late decelerations, perinatal asphyxia occurred within a short time, as early as within 10 minutes of prolonged deceleration. Morbidity was minimal when delivery occurred within 13 minutes from onset of prolonged deceleration [68].

Maternal cardiopulmonary arrest

The extent of neonatal asphyxia following maternal cardiopulmonary arrest depends upon numerous factors independent of the time factor including the etiology of the collapse, maternal state and physiologic stability / instability prior to collapse, and gestational age of the fetus. In a review from the national registry of maternal collapse with a live fetus, neurologically intact survival was inversely related to the time from cardiac arrest to delivery [68].

A reivew of published data of neonatal outcome following maternal death between 1900 to 1985, found that the most fetal survivors were delivered within 5 minutes and none survived 10 minutes after maternal demise [69].

Crucial delivery time

AAP / ACOG have emphasized a 30 minute time interval from decision to delivery (cesarean section) [69, 70]. Most medical centers in USA provide necessary facilities including presence of qualified obstetricians, pediatricians, operating rooms, anesthesia, and nursing support. However, in the event of catastrophic emergency, extent of fetal hypoxic ischemic state and neurologic damage is virtually unpredictable and often not related to event-delivery time.

Fetal factors

Multiple pregnancy and CP

Multiple pregnancy contributes disproportinately to the incidence of CP. In fact 2.4% of multiples contribute to 25% of children with CP. Prevalence of CP in multiples is epidemoiologically quoted to be 7/1000 births, and the probability of at least one child with CP from a multiple pregnancy is 15/1000 for twins, 80/1000 for triplets, and 429/1000 for quadruplets. Association of preterm birth, low birth weight, discordant growth, birth order, monozygocity, monochorionicity, and intrauterine demise of one fetus all predispose these babies to CP.

Preterm births

The overall risk of CP in twins weighing > 2500 g is 3.38 times more than singletons of similar birth weight. In a recent study, relative risk (RR) for CP in a comparison of similar birth weight was 4.5 (95% CI), while RR in comparison of

gestational age of > 37 weeks was 6.3 (95% CI). Multiplicity of fetus itself appears to be a risk factor for CP [71-73].

Monochorionicity and demise of one

Monozygotic and monochorionic twins are more likely to result in neurologic abnormalities than others due to vascular anastomoses, fetal growth problems, and cord abnormalities. This risk is higher for the survivor when demise of one occurs in a monochorionic gestation [74,75].

A recent study investigating antenatal origin of neurologic injury by ultrasound assessment of neonatal brain revealed cerebral atrophy and white matter necrosis to occur more often in monochorionic twins than in dichorionic twins (30% vs 3.3%, P<0.001) [76]. Polyhydramnios, demise of one, and vascular abnormalities within the placenta all played a role in increasing this risk.

The most outstanding pathologic lesions in the surviving twin in a monochorionic pregnancy complicated by demise of one include renal cortical necrosis and multicystic encephalomalacia. These processes occur due to intraplacental vascular connections. Major placental vascular connections allow twin to twin transfusion (TTS) to occur leading to the syndrome of TTS due to uncompensated vascular anastomoses and imbalanced distribution of blood between the twins. Often extreme degree of transfusion may predispose one or the other twin to severe decompensation ultimately resulting in CP.

Multiple pregnancy is independent risk factor for neurologic deficit and CP. Monochorionicity and demise of one twin predispose twins to even greater risk of neurologic impairment.

Intrauterine growth retardation (IUGR) vs small for gestational age infant (SGA)

These terms refer to a baby with a birth weight less than an average weight for comparable gestational age. IUGR refers to a pathophysiologic state resulting in small size while SGA is simply a small birth weight baby. Birth weight of the baby in question is compared to a standard nomogram of birth weight in the community.

In US, standard nomograms for females and males are available [77,78]. A baby falling below the 10th percentile is considered SGA. However, adverse perinatal outcome and consequently risk of encephalopathy and even mortality rises for newborns weighing below the 5th and specially below the 3rd percentile for age [9,79]. Relative risk of encephalopathy for birth weights below the 3rd percentile when compared to those between 3rd to 9th percentile is significantly greater (OR 38.23 vs 4.37) and so also when compared to those above the 9th percentile (OR 1.54). Arrest of fetal growth or loss of weight are distinct but imprecise measures of fetal risk.

Numerous other variables may determine the ultimate outcome and risk of encephalopathy eg. perinatal infections, genetic and structural abnormalities, substance abuse, coagulopathies etc.. An IUGR infant born preterm has obviously much greater risk.

National Collaborative Perinatal Project found infants without any hypoxia related risk factors not to be at increased risk for neurologic morbidity or CP. Conversely, IUGR newborns with hypoxia related risk factors were more likely to have neurologic deficits [80]. Oligohydramnios and IUGR combination suggesting chronic fetal hypoxia may also result in fetal cerebral ischemia and white matter lesions [81,82]. Adverse developmental outcome with IUGR/SGA in otherwise healthy babies results from nonnutritional causes. Etiologies of IUGR are multiple and determine the ultimate outcome. No interventions other than delivery have any impact on outcome of IUGR.

Postterm birth / Postmaturity syndrome

Perinatal mortality increases after 41 weeks of gestation. A significant increase in RR for encephalopathy beyond 39th week of gestation was found in a large population based study (RR 1.41 at 40, 3.34 at 41, and 13.2 at 42 weeks of gestation) [9]. Currently in US, postdate fetuses routinely undergo biweekly heart rate surveillance by NST and are delivered by 42 weeks.

Meconium passage

Passage of meconium was implicated as a marker for new born hypoxia/asphyxia. It has been found to be a poor predictor of HIE. A review of 42,000 term singletons did not find any increased incidence of adverse neonatal findings in newborn with meconium stained fluid [83,84]. Vasoconstriction of cord vessels leading to hypoxia due to meconium has been theorized. It has not been confirmed scientifically and 99.6% of term fetuses with meconium stained fluid do not have CP. In fact, Meconium passage is a physiologic event and by itself is not a marker for fetal hypoxia. It may form a nidus for bacterial growth in the amniotic cavity.

Genetic, anatomic, and metabolic etiologies of neonatal encephalopathy

Neonatal altered neurologic manifestations can occur as a result of genetic, metabolic, and anatomic etiology, and may contribute to neonatal encephalopathy [85,86]. Many of these disorders result in hypoglycemia, hyperammonemia or other metabolites leading to irreversible metabolic, anatomic or

functional effects and adversely affect the brain structure and/or function. Table 3 gives the congenital disorders associated with neonatal encephalopathy / CP.

Table 3. Congenital disorders associated with neonatal encephalopathy / cerebral palsy.

Neonatal hypoglycemia
Hyperammonemia
Disorders of aminoacid metabolism
Organic acid abnormalities
Degenerative diseases of nervous system
Lower motor neuron disorders
Anatomic abnormalities of CNS
Chromosomal abnormalities
Neuronal migration disorders presenting as CP

Table 4. Severe recurrent or persistent neonatal hypoglycemic conditions.

Endocrine deficiencies

- Panhypopituitarism
- Isolated growth hormone deficiency
- Cortisol deficiency (adrenocorticotropic hormone unresponsiveness, isolated glucocorticoid deficiency, maternal steroid therapy, adrenal hemorrhage, adrenogenital syndrome)
- Hypothyroidism
- Glucagon deficency

Hyperinsulinism

- Beckwith-Wiedemann syndrome
- Macrosomia (without Beckwith-Weidemann syndrome)
- B-cell nesidioblastosis - adenoma spectrum
- Functinal B-cell hyperplasia (without nesidioblastosis or adenoma)
- Leucine sensitivity

Hereditary metabolic defects

- Carbohydrate metabolism (galactosemia, glucose-6-phosphatase deficiency (von Gierke disease), glycogen synthetase deficiency, frutose-1,6-diphosphatase deficiency, phosphoenopyruvate carboxykinase deficiency, pyruvate carboxylase deficiency)
- Aminoacid metabolism (maple syrup urine disease, hereditary tyrosinemia)
- Organic acid metabolism (propionic academia, methylmalonic academia)
- Fatty-acid metabolism (medium- and long-chain acetyl-CoA dehydrogenase deficiencies).

Adapted from Volpe JJ. Hypoglycemia and brain injury. In : Neurology of the new born. 4th edn. Philaddhia. WB Saunders. 2001:497-52.

Neonatal hypoglycemia

Neonatal hypoglycemia may occur as a result of hyperinsulinism, endocrine deficiencies, or metabolic defects and produce neuronal as well as glial injury. Table 4 lists the various conditions causing neonatal hypoglycemia.

Conclusions

CP is caused by myriad different etiologies. Presence of neonatal hypoxic ischemic encephalopathy is essential for it to be of intrapartum origin. Since large number of cases occur as a result of antepartum events and genetic, chromosomal, familial, and inherited etiologies oportunities for prevention are limited. Management of obstetrical reasons such as prematurity, hypoxia, cord accidents, third trimester bleeding etc., may be amenable to limited preventive measures.

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References

1. Stanley F, Blair E, Alberman B. How common are the cerebral palsies ? In : Stanley F, Blair E, Alberman B (eds). Cerebral Palsies : Epidemiology and Causal Pathways. London, MacKeith Press;2000:22-48.
2. Blair E, Stainley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. J. Pediatr 1988;112:515-9.
3. Neslon KB, Ellenberg JH. Antecendents of cerebral palsy, multivariate analysis of risk. N Engl J Med 1986;315:81-6.
4. Yudkin PL, Johnson A, Clover LM et al. Clustering of perinatal markers of birth asphyxia and outcome at age five years. Br J Obstet Gynaecol 1994;101:774-81.
5. MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. BMJ 1999;319:1054-9.
6. Neonatal encephalopathy and cerebral palsy. Defining the pathogenesis and pathophysiology 2003: a report by the Task Force American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. Washington, DC. ACOG.2003.
7. Phelan JP, Korst LM, Ock AM et al. Neonatal nucleated red blood cell and lymphocyte counts in fetal brain injury. Obstet Gynecol 1998;91:485-9.
8. Saracoglu F, Sahin I, Eser E et al. Nucleated red blood cell as a marker in acute and chronic fetal asphyxia. Int J Gynecol Obstet 2000;71:113-8.
9. Badawi N, Kurinczuk JJ, Keogh JM et al. Antepartum risk factors for newborn encephalopathy; the Western Australian case-control study. BMJ 1998;317:1549-53.
10. Nelson KB, Ellenberg JH. Obstetric complications as risk factors for

cerebal palsy or seizure disorders. JAMA 1984;251:1843-8.

11. Nelson KB, Grether JK. Potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight. Am J Obstet Gynecol 1998;179:507-13.
12. Adamson SJ, Alessandri LM, Badawi N et al. Predictors of neonatal encephalopathy in full term infants. BMJ 1995;311:598-602.
13. Topp M, Langghoff-Roos J, Uldall P. Preterm birth and cerebral palsy. Predictive value of pregnancy complications, mode of delivery, and Apgar scores. Acta Obstet Gynecol Scand 1997;76:843-8.
14. Nelson KB, Willowghby RE. Infection, inflammation and the risk of cerebral palsy. Curr Opin Neurol 2000; 13:133-9.
15. Eastman NJ, DeLeon M. The etiology of cerebral palsy. Am J Obstet Gynecol 1955;69:950-61.
16. Grether JK, Nelson KB. Maternal infection cerebral palsy in infants of normal birth weight. JAMA 1997:278:207-11.
17. Keogh JM, Badawi N, Kurinczuk JJ et al. Group B streptococcus infection, not birth asphyxia.Aust NZJ Obstet Gynecol 1999;39:108-10.
18, Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy. A meta-analysis. JAMA 2000;284:1417-24.
19. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500-7.
20. Eschenbach DA. Amniotic fluid infection and cerebral palsy (editorial). Focus on the fetus. JAMA 1997;278:247-8.
21. Yoon BH, Romero R, Kim CJ et al. High expression of tumor necrosis factor-alpha and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol 1997;177:406-11.
22. Gomez R, Romero R, Ghezzi F et al. The fetal inflammatory response syndrome. Am J Obstet Gynecol 1998;179:194-202.
23. Yoon BH, Romero R, Yang SH et al. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. Am J Obstet Gynecol 1996;174:1433-40.
24. Baud O, Emilie D, Pelletier E et al. Amniotic fluid concentrations of interileukin-1 beta, interelukin-6 and TNF-alpha in chorioamnionitis before 32 weeks of gestation: histological associations and neonatal outcome. Br J Obstet Gynaecol 1999;106:72-7.
25. Grether JK, Nelson KB, Dambrosia JM et al. Interferons and cerebral palsy. J Pediatr 1999:134:324-32.
26. Nelson KB, Dambrosia JM, Grether JK et al. Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol 1998;44:665-75.
27. Shrag SJ, Zywicki S, Farley MM et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N. Engl J Med 2000;342:15-20.
28. Baker CJ. Group B streptococcal infection in new borns: prevention at last ? (editorial). N Engl J Med 1986;314:1702-4.
29. Klein J. Bacterial sepsis and meningitis. In : Remington JS, Klein J. Infectious diseases of the fetus and newborn infant. 5th edn. Philadelphia, WB Saunders. 2001;943-98.
30. Mittendorf R Covert R, Kohn J et al. The association of coagulase - negative staphylococci isolated from the chorioamnion at delivery and subsequent development of cerebral palsy. J. Perinatol 2001;21:3-8.
31. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the palcenta : cerebral thrombi and infarcts, coagulopathies and cerebral palsy. Hum Pathol 1999;30:759-69.
32. Grafe MR. The correlation of prenatal brain damage with placental pathology. J Neuropathol Exp Neurol 1994;53:407-15.
33. Salafia CM, Parke AI. Placental pathology in systemic lupus erythematosus and phospholipid antibody syndrome. Rheum Dis Clin North Am 1997;23:85-97.
34. Thorarensen O, Ryan S, Hunter J et al. Factor V Leiden mutation: an unrecognized cause of hemiplegic cerbral palsy, neonatal stroke, and placental thrombosis. Ann Neurol 1997;42:372-5.
35. Nelson KB. Ellenberg JH. Antecedents of cerebral palsy. 1. Univariate analysis of risks. Am J Dis Child 1985;139:1031-8.
36. Badawi N, Kurinczuk JJ, Mackenzie CI et al. Maternal thyroid disease: A risk factor for newborn encephalopathy in term infants. BJOG 2000;107:798-801.
37. Reuss ML, Paneth N, Pinto-Martin JA et al. The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. N Engl J Med 1996;334:821-7.
38. Lucas A, Ronnie J, Baker BA et al. Low plasma triidothyronine concentrations and outcome in preterm infants. Arch Dis Child 1088;63:1201-6.
39. Osborn DA. Thyroid hormones for preventing neurodevelopmental impairment in preterm infants (Cochrane Review) In : The Cochrane Library Issue 4; 2001. Oxford UPdate; Update; Update software (Meta-analysis).
40. Jones KL, Smith DW, Ullelnad CN et al. Pattern of malformation in offspring of chronic alcoholic mother Lancet 1973;1:1267:71.
41. American Academy of Pediatrics. Committee on Substances Abuse and Committee on Children with Disabilities. Fetal alcohol syndrome and alcohol related neurodevelopmental disorders. Pediatrics 2000;106:358-61.
42. Chasnoff IJ, Bussey ME, Savich R et al. Perinatal cerebral infarction and maternal cocaine use. J Pediatr 1986;108:456-9.
43. Lumley J, Lester A, Anderson I et al. A randomized trial of weekly cardiotocography in high-risk obstetric patients. Br J Obstet Gynaecol 1983;90:1018:26.
44. Flynn AM, Kelly J, Mansfield H et al. A randomized controlled trial of non-stress antepartum cardiotocography. Br J Obstet Gynaecol 1982;89:427-33.
45. Neldam S. Fetal movements as an indicator of fetal well being. Lancet 1980:1222-4.
46. Beischer NA, Drew JH, Ashton PW et al. Quality of survival of infants with critical fetal reserve detected by antenatal cardiotocography. Am J Obstet Gynecol 1983;146:662-70.
47. Manning FA, Bondaji N, Harman CR et al. Fetal assessment based on fetal biophysical profile scoring VIII. The incidence of cerebral palsy in tested and untested perinates. Am J Obstet Gynecol 1998;178:696-706.
48. Haverkamp AD, Thompson HF, McFee CC. The evaluation of continuous fetal heart rate monitoring in high-risk pregnancy. Am J Obstet Gynecol 1976;125:310-20.
49. Haverkamp AD, Orleans M, Langendoerfer S et al. A controlled trial of differential effects of intrapartum fetal monitoring. Am J Obstet Gynecol 1979;134:399-412.

50. Kelso IM, Parsons RJ, Lawrence GF et al. An assessment of continuous fetal heart rate monitoring in labor. A randomized trial. Am J Obstet Gynecol 1978;131:526-32.

51. McDonald D, Grant A, Sheridan-Periera M et al. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring Am J Obstet Gynecol 1985;152:524-39.

52. Renou P, Chang A, Anderson I et al. Controlled trial of fetal intensive care. Am J Obst Gynecol 1976;126:470-6.

53. Wood C, Renou P, Oates J et al. A controlled trial of fetal heart rate monitoring in a low-risk obstetric population. Am J Obstet Gynecol 1981;141:527-34.

54. Grant A. Epidemiological principles for the evaluation of monitoring programs - the Dublin experience. Clin Invest Med 1993;16:149-58.

55. Thacker SB, Stroup DF, Peterson HB. Efficacy and safety of intrapartum electronic fetal monitoring : An update. Obstet Gynecol 1995;86:613-20.

56. Garite TJ, Dildy GA, McNamara H et al. A multicenter controlled trial of fetal pulse oxymetry in the intrapartum management of nonreassuring fetal heart rate patterns. Am J Obstet Gynecol 2000;183:1049-58.

57. Zuspan FP, Quilligan EJ, Iams JD et al. Predictors of intrapartum fetal distress: the role of electronic fetal monitoring. Report of the National Institute of Child Health and Human Development Consensus Development Task Force. Am J Obstet Gynecol 1979;135:287-91.

58. Nelson KB, Dambrosia JM, Ting TY et al. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. N Engl J Med 1996;334:613-8.

59. Roland EH, Poskitt K, Rodriguez E et al. Perinatal hypoxioischemic thalamic injury: clinical features and neuroimaging. Ann Neurol 1998;44:161-6.

60. Pasternak JF, Gorey MT. The syndrome of acute near total intrauterine asphyxia in the term infant. Pediatr Neurol 1998; 18:391-8.

61. Phelan JP, Ahn MO, Korst L et al. Intrapartum fetal asphyxial brain injury with absent multiorgan system dysfunction. J Matern Fetal Med 1998;7:19-22.

62. Woo JS, Ngan YS, Ma HK. Prolapse and presentation of the umbilical cord. Aust NZJ Obstet Gynaecol 1983;23:142-5.

63. Niswander KR. Friedman EA, Hoover DB et al. Fetal morbidity following potentially anoxigenic obstetric conditions. III. Prolapse of the umbilical cord. Am J Obstet Gynecol 1966;95:853-9.

64. Niswander KR, Friedman EA, Hoover DB et al. Fetal morbidity following potentially anoxigenic obstetric conditions. IV. Occult prolapse of the umbilical cord. Am J Obstet Gynecol 1966;95:1099-103.

65. Murphy DJ, MacKenzie IZ. The mortality and morbidity associated with umbilical cord prolapse. Br J Obstet Gynaecol 1995;102:826-30.

66. Leung AS, Leung EK, Paul RH. Uterine rupture after previous cesarean delivery: maternal and fetal consequences. Am J Obstet Gynecol 1993;169:945-50.

67. Clark SL, Hankins GD, Dudley DA et al. Amniotic fluid embolism : analysis of the National Registry. Am J Obstet Gynecol 1995;172:1158:67;discussion 1167-9.

68. Katz VL, Dotter DJ, Droegemueller W. Perimortem cesarean delivery Obstet Gynecol 1986;68:571-6.

69. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Intrapartum and Postpartum care of women. In : Guidelines for perinatal care. 5th edn. Elk Grove Village (II): AAP: Washington (DC). 2002:124-61.

70. Freeman JM, Nelson KB. Intrapartum asphyxia and cerebral palsy. Pediatrics. 1988;82:240-9.

71. Grether JK, Nelson KB, Cummins SK. Twinning and cerebral palsy: experience in four northern California counties births - 1983 through 1985. Pediatrics 1993;92:854-8.

72. Patterson B, Nelson KB, Watson L et al. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. BMJ 1993;307:1239-43.

73. Williams K, Hennessy E, Alberman E. Cerebral palsy : effects of twinning, birth weight, and gestational age. Arch Dis Child Fetal Neonatal Ed 1996;75:F178-F182.

74. Fusi I, Gordon H. Twin pregnancy complicated by single intrauterine death.Problems and outcomes with conservative management. Br J Obstet Gynaecol 1990;97;511-6.

75. Sehr AL, Patterson B, Blair E et al. The risk of mortality or cerebral palsy in twins : a collaborative population based study. Pediatr Res 2002;52:671-81.

76. Petersen IR, Nyholm HC. Multiple pregnancies with single intrauterine demise. Description of twenty-eight pregnancies. Acta Obstet Gynecol Scand 1999;78:202-6.

77. Alexander GR, Himes JH, Kaufman RB et al. United States national reference for fetal growth. Obstet Gynecol 1996;87:163-8.

78. Hadlock FP, Harrist RB, Carpenter RD et al. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. Radiology 1984;150:534-40

79. McIntire DD, Bloom SL, Casey BM et al. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999;340:1234-8.

80. Berg AT. Indices of fetal growth retardation, perinatal hypoxia related factors and childhood neurological morbidity. Early Hum Dev 1989;19:271-83.

81. Giles FH, Leviton A, Dooling EC. The developing human brain : growth and epidemiologic neuropathology. Boston: John Wright 1983.

82. Sims ME. Turkel SB, Halterman G et al. Brain injury and intrauterine death. Am J Obstet Gynecol 1985;151:721-3.

83. Nathan L, Leveno KJ, Carmody TJ et al. Meconium : a 1990s perspective on an old obstetric hazard. Obstet Gynecol 1994;83:329-32.

84. Dijxhoorn MJ, Visser GH, Fidler VJ et al. Apgar score, meconium and acidemia at birth in relation to neonatal neurological morbidity in term infants. Br J Obstet Gynaecol 1986;93:217-22.

85. Badawi N, Watson L, Petterson B et al. What constitutes cerebral palsy ? Dev Med Child Neurol 1998;40:520-7.

86. Burton BK. Inborn errors of metabolism in infancy : a guide to diagnosis. Pediatrics 1998;102:E69.