Revisiting Cerebral Palsy: Pathogenesis and Management

ABSTRACT

Brain damage in utero and its consequences in neonates especially cerebral palsy (CP), are socially disturbing and psychologically distressing to both patients and carers. The prevalence of CP has not declined considerably despite several preventive measures in obstetric and neonatal care. Current views on the pathogenesis and causal pathways of CP relate to hypoxic-related ischemic events. A series of cascading events trigger the inflammatory processes resulting in gliosis of the white matter when labor and the delivery processes are reviewed. Though animal studies seem to support these concepts several other causes like perinatal infection and prematurity are also strong contributors to its pathogenesis. Multiple gestation and genetic factors may play a role in the etiology.

Current management strategies focus on preventive measures during antenatal and intrapartum care. The use of antenatal steroids, magnesium sulfate infusion for cerebral protection and the extensive use of electronic fetal monitoring during labor have been elaborated as deliberate attempts to minimize the impact of any of the possible contributing cause. As CP is still prevalent in pediatric practice and in our community discussing means to improve prognosis of affected children are relevant.

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INTRODUCTION

Cerebral palsy (CP) is a common childhood disorder that has devastating consequences on the child, caretakers and health resources. It is a neurological impairment of control of movement and posture that constitutes multiple entities. Four core components define the condition that is acquired in early life, resulting from abnormalities in brain development. Conventional teaching refers to clinical manifestations of CP being related to disorders in movement and posture that are static at the time of presentation. The current definition is debatable as several dynamic factors impact on the condition as the child develops in age. Elements of intellectual capacity may not be identifiable till at a later age1,2 (Fig. 1).

First described by William John Little in 1843, CP was erroneously linked to specific complication of labor including difficult labor, asphyxia and prematurity.3 Case control studies conducted in different geographical locations on intrapartum fetal asphyxia causing CP, however, are relatively contradictory.4,5 Although a population-based study quoted that one in every three cases of CP has had at least one adverse event during birth, it could not eliminate other factors that may contribute to CP, like preterm birth, maternal or neonatal infection.6 It is becoming increasingly clear that the etiology of CP is varied but what is more apparent is that it is an abnormality of brain development or an acquired nonprogressive cerebral lesion. The belief that it is solely related to intrapartum hypoxia is not supported by evidence as 90 to 95% of the disabilities seen in CP are rarely related to labor.4 A systematic review by Graham et al showed that a vast majority of CP was not associated with intrapartum hypoxic-ischemia.7

Over the last three decades, improvements in intrapartum care has resulted in a marked reduction of perinatal mortality in infants going through intrapartum complications but this does not translate in marked reduction in prevalence of CP.5

ETIO PATHOGENESIS

In clinical practice, it is well recognized that the cause of CP is not known in many affected children. Neuroimaging studies have been helpful in assigning possible causes of CP. A recent review of babies born between year 2003 and 2006 in Sweden showed the prevalence of CP remained the same at about 2.2/1000 live births but changing patterns were evident. Of the 206 cases of CP maldevelopment, white matter lesion, corticosubcortical lesion and basal ganglia lesions occurred in 13, 36, 23 and 14% respectively.5
It is prudent to review the fundamentals of brain development to support the varied etiology implicated in CP. Although the brain continues to develop beyond 10 years of age, some of the factors contributing to CP may be present at a very early age of embryological development. What is commonly known is that a defect in formation of the neural tube results in neural tube defect within 30 days of conception. Neuronal migration defects occur in the fetus between 7 and 16 weeks when the nerves migrate from the germinal layer of the ventricles out to the cerebral cortex and central nuclei. Any brain insult during this phase of development could result in cortical dysplasia or polymicrogyria. After about 28 weeks gestation, further maturation is seen with glial cell migration into the white matter resulting in adequate myelination, a process that continues till adult life. Of interest to obstetric care is the fact that the white matter is vulnerable to severe hypoxia between 28 and 36 weeks, paving the way for an understanding of the linear association of CP with prematurity.9-11

On the other hand, hypoxic-ischemia affecting the gray matter is more prevalent with increasing gestational age because of the branching vascular supply that curtails flow to the ‘watershed zone’.12,13

Gestational age, brain development, vascular supply, nature of brain insult and vulnerable areas affected by pathology depicts the nature of disability in later life. This principle also permits one to relate to the common causes of CP often quoted and the conditions associated with CP in obstetric practice like severe prematurity, maternal intrauterine infections, intrauterine growth restriction and pre-eclampsia, or acute hypoxic-ischemia due to prolapse of the umbilical cord, abruptio placenta and uterine rupture. Observational and necropsy studies indicate that about 20% of white matter injury is related to a vascular etiology.5,14 The severity of cerebral injury is dependent on the development and anastomoses of short and long vessels that penetrate either the periphery or deep periventricular areas at different gestational age. This vasculature is less complete before 32 weeks explaining the higher impact of injury in premature infants.15

CAUSAL PATHWAYS

Obstetric practices, especially interventions during labor, have been erroneously linked with development of CP. The myriad of factors currently reported to be associated with CP appear to relate to developmental disorders and other insults long before intrapartum events. However, there is a small group of patients where CP would be an effect of intrapartum hypoxia in labor. An international group categorically included spastic quadriplegia or athetoid CP as vital in linking the disorder to obstetric practice.16,17 A majority of fetuses affected by CP have had brain insults long before labor sets in. This fact is defended by the remarkable defense mechanism the term fetus has, e.g. fetal hemoglobin releases more oxygen than adult hemoglobin, and the ability of the acutely stressed fetus to redistribute nearly all its blood supply to the brain and placenta.

The embryological development described above where brain insults in various forms can affect its function and results from animal studies. Reiterate the possible sites of the brain that can be affected by hypoxic-ischemia. The basal ganglia, thalami and inferior colliculi appear to be damaged severely within 10 to 16 minutes when hypoxic ischemia is induced in animal models.18,19 Researchers continue to argue as to the reproducibility of adverse findings seen in animals, including primates to nonanesthetized human fetuses. As alluded CP is not a disease of intrapartum induced hypoxia in a majority of cases as developmental disorders like cerebral dysgenesis, intrauterine infections, genetic, metabolic or toxic factors have been implicated20 (Table 1).

Effect of Prematurity and Low-birth Weight

McDonald’s observational study in 1963 convincingly shows the association of prematurity on the eventual development of CP.21,22 Williams CE et al (1992) have shown a classic progressive involvement of the nine brain regions with increasing duration of ischemia ranging from 0 to 40 minutes, with the parasagittal cortex showing higher neuronal scores compared to the thalamus, the latter being affected least.23 Cystic periventricular leucomalacia (focal and diffuse) and periventricular

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<td>• Severe prematurity and extreme low-birth weight</td>
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hemorrhage are precursors for the subsequent adverse outcomes. Although this is simplistically stated, the series of events described makes the immature brain of the preterm fetus more vulnerable than the term fetus. Although the immature brain is highly vascular, the vessels have ‘deficient muscular coat’ (26 weeks gestation) permitting rupture of the capillary network with acute or chronic injury. Molecular biology throws further insights in our understanding of how blood vessel development is closely involved in brain development and maldevelopment. Storkebaum et al insights into the role of blood vessels in cerebrovascular disorders clearly points out that blood vessels do not remain ‘neutral bystanders in the development of CP and other neurodevelopmental disorders of the fetus and new born need to be factored in.’

Premature births have been characteristically associated with development of CP with the extremely low-birth weight (ELBW) neonate being worst affected. Prevalence of CP ranging from about 50 to 70 per 1000 live births and 35 to 80 per 1000 live births among those born between 28 and 31 weeks in population studies would alert care givers about the perceived increase in CP among survivors because of the improvements in neonatal care for the severely premature babies in most developed and developing countries. Though term and post-term newborn babies contribute to half of the overall proportion of CP case, the rate is estimated to be the lowest at 0.99 per 1000 birth at 40 weeks with increased frequency at earlier (37 weeks) or later (42 weeks) gestation with relative risk of 1.4 to 1.9. Low gestational age is the most important risk factor for CP. Concomitant occurrence of inflammation in severe prematurity appears to compound the problem. Evidence of infection using 24 inflammatory markers showed that an increased risk of CP at the end of 24 months when inflammatory markers persisted beyond 3 days of birth in infants born below 28 weeks gestation.

Multiple Gestation

Multiple gestation has also been associated with 15 times increased risk of CP compared to singleton pregnancies adjusted for gestation and weight. Multiple pregnancies encompass antenatal complications like preterm birth, low birth weight infants, death of a co-twin and birth defects in one or more infants which are known to correlate with occurrence of CP. The prevalence is quoted to be much higher in monochorionic placentation which is said to correlate with multiple vascular anastomoses in the placenta. A longitudinal study by Lopriore et al of 33 multiple pregnancies with twin to twin transfusion syndrome found the incidence of CP to be as high as 21% the 29 infants who survived after 6 years. It was even higher in infants after the intrauterine demise of a co-twin and serial amnioreduction.

Infection

Intrauterine infection is accompanied by inflammatory processes with production of cytokines in the uterine cavity or membrane initiating uterine contractions with or without rupture of membrane leading to birth. Inflammation and cytokines are implicated especially in chorioamnionitis or ascending infection from maternal sources like pyelonephritis resulting in premature birth caused by preterm premature rupture of membrane (PPROM) or prolonged rupture of membrane. Leviton’s proposal implicating the adverse effect of cytokines on the brain and TNF-alpha causing both hypotension (which inadvertently leads to hypoxic-ischemia and DIVC) and concurrent endothelial damage (role of platelets activation factor and its cytotoxic effect) results in bad outcome, i.e. in both destruction of oligodendrocytes and proliferation of astrocytes. However, it is felt that the intensity of infection is more likely to be associated with injury to the brain besides other potential predisposing factors like low gestational age, vulnerability of the blood vessels, and integrity of blood-brain barrier and intensity of infection.

A variety of neonatal infections (viral, bacterial, parasitic and fungal) are implicated in CP causing direct damage to the brain or a massive shock inducing systemic inflammatory response and multisystem failure. Many studies indicate the association between maternal infection and CP but with different pathophysiology. The infected new born may suffer septic shock, meningitis or pneumonia resulting in pulmonary hypertension, perinatal asphyxia and brain damage by the proinflammatory cytokines. The risk increases four-fold in premature infants born before 32 weeks gestation. It is also true for term babies born to mothers with clinical chorioamnionitis with a relative risk of 4.7. Yoon et al showed the central role inflammation plays in development of periventricular leukomalacia, the important link to CP. They demonstrated that inflammatory cytokines in cord blood released as a consequence of intrauterine infection play a vital role in the genesis of preterm delivery, fetal PVK and CP.

Genetic Influence

As CP is a nonspecific clinical diagnosis, it is possible that individuals with a wide range of neurodevelopmental abnormalities may go undetected. Although neuroimaging modalities like magnetic resonance imaging (MRI) can detect anatomical lesions, more specific biochemical or molecular diagnostic testing need to be developed for establishment of cause-effect relationship. Genetic factor
as a cause has been studied for its association to increased risk of CP. Some population-based studies claim that there is no statistically significant difference in CP prevalence in various ethnic groups. Other studies on genetic polymorphism and its correlation with CP showed that factor V Leiden mutation or methylenetetrahydrofolate reductase (MTHFR) gene mutation in thrombophilia, when present in combination, increases the risk of displegic type CP in preterm infants. It was also found that CP occurs 2.5 times higher in consanguineous family; a significantly higher concordance rate for CP in monozygotic than dizygotic twins, higher prevalence of congenital anomalies in individuals of CP than the general population and the identification of several single-gene mutations in idiopathic CP pedigrees.

Consequently, it is generally acceptable that the clinical diagnosis of CP should be made after the exclusion of genetic and metabolic disorders. However, it is not often that comprehensive genetic testing is offered to patients with suspected CP leading to misdiagnosis and possible delay in treatment. There are potential genomically guided therapeutic interventions in dystonic disorders which are related to gene mutations like in GTP cyclohydrolase 1, sepiapterin reductase and tyrosine hydroxylase.

Intrapartum Hypoxia

Differing views have been expressed pertaining to brain injury in neonates resulting from hypoxic events during intrapartum period. The diagnosis of CP should be based on clinical findings meeting four criteria, i.e. evidence of metabolic acidosis (umbilical artery pH < 7 and base deficit ≥ 12 mmol/l at delivery), early onset of severe or moderate neonatal encephalopathy in infants born at ≥ 34 weeks of gestation, CP of the spastic quadriplegic or dyskinetic type and exclusion of other identifiable etiologies, e.g. trauma, coagulation disorders, infection and genetic disorders (Fig. 2).

The causal association between CP and intrapartum hypoxia is rather difficult to prove. Epidemiological studies in the past showed that 90% of CP were not related to intrapartum hypoxia and the 10% of cases that had any causal relation to the damaging effects of hypoxia were related to either antenatal or intrapartum events. A study in Sweden quoted as high as 58% events of CP were related to birth asphyxia. Some perinatal events showed high odds ratio for CP like vaginal breech delivery, abruptio placenta, instrumental delivery, emergency cesarean delivery and post-term delivery. All these events were related to indicated delivery or urgency of delivery.

Neuroimaging has played an important role in determining the timing of injury and relationship to CP in determining plausible pathogenesis mainly to rule out progressive or genetic disorders as well as evaluating severity of the condition. However, controversies remain as there is little evidence to support the use of MRI technique in detecting hypoxic-ischemia as a cause of CP. Generally, neuroimaging studies report high abnormalities of almost 80% in children with CP involving the commonest periventricular leukomalacia, gray matter lesion and some other brain abnormalities. It can nevertheless provide some understanding of the pattern and severity of brain injury, allowing early intervention to reduce occurrence of CP in high-risk patients.

Cranial ultrasound is increasingly adopted as a non-invasive diagnostic test enabling detection of echolucent lesions which is seen in 52% of extremely premature and low birth weight babies with CP. However, there is no conclusive evidence in determining the actual timing and contribution of hypoxic-ischemic event leading to CP. Changes occurring in the brain may manifest later in neonate life making it difficult to invoke a causal-effect relationship. The extent of abnormalities detected does not reflect the true severity or type of motor dysfunction. Doppler velocimetry studies have been attempted since the early 90s to determine the relationship between formations of cystic lesion in the brain of CP children during conception.

The principle of detecting the velocimetry of blood flow of interrogated blood vessels has shown an inverse correlation with the extent of neuronal damage in some studies. Nevertheless, it would not measure the content of oxygen delivered via the vessels to watershed areas, a vital fact impacting pathogenesis. The importance of neuroimaging findings reflecting on cause of CP is unfortunately outweighed by plausible explanations based on the principle of inflammatory phenomena in the etiology of CP.
PREVENTION OF CEREBRAL PALSY: IS THIS POSSIBLE?

Preventive strategies, though difficult, are worthy of revisit. Clinicians appear to tread on unknown completely convincing explanations when one tries to change clinical practice based on both animal and human studies. The extensive use of electronic fetal monitoring and dependence of fetal scalp blood sampling have their advantages but have severe limitations in predicting the subsequent development of CP. If a large proportion of etiology of CP is related to antenatal factors, preventive strategies need to be directed to correctable factors. Current resources and clinical determinants unfortunately do not permit such intervention. Strategies to prevent premature birth and extreme low birth weight babies require a broader socioeconomic approach. Intrauterine infections often are detected late and it is doubtful if effective intervention could avoid damage.

Electronic Fetal Monitoring and Its Role in Detecting Early Fetal Hypoxia at Intrapartum Period

Though intrapartum hypoxic events contribute to a very low incidence of CP, current available fetal surveillance techniques need to be optimally utilized to detect early onset of damaging hypoxia to the fetal brain. Fetal surveillance in labor with routine electronic monitoring has had minimal impact in prevention but is warranted in avoidance of hypoxic injuries. The CTG remains a common tool for monitoring the fetus in labor. Attempting to correlate CTG changes to hypoxic ischemic insult remains a challenge especially when the eventual outcome is CP. Timing an insult to relate to adverse neurological outcomes in severe bradycardia (<80 beats/min) in term fetuses among those who eventually had CP indicated that the shortest time for damage to the deep gray matter was 14 minutes. One then can infer that such arbitrary duration does not reflect on observational studies where CP is associated with hypoxic-ischemic events.

It is pertinent that determining causation directly related to intrapartum events is difficult. Hence, common sense must prevail in using terms like ‘fetal distress’ and ‘birth asphyxia’. Even in the immature brain, following acute or chronic injury neuronal or white matter loss takes days to weeks to occur and this fact makes it difficult to determine the exact timing of original neurological insult. Preterm births are at risk of CP as 85% of those less than 32 weeks (<1500 gm) survive; of these 10% go on to develop spastic motor deficit; cognitive and behavioral problems are seen in up to 50%.59

Antenatal Strategies and Neonatal Support

A single dose of antenatal steroid has been accepted as a beneficial measure to reduce intraventricular hemorrhage and acute respiratory distress syndrome in premature infants at risk. It was reported that corticosteroids inhibit cytokines production and potentially prevent white matter injury in the presence of intrauterine infection or inflammation reducing the morbidity or mortality associated with extreme prematurity.60 Opinions are mixed about the appropriate frequency of administration and dosage of steroids when involving pregnancies with multiple gestation or extreme low-birth weight fetuses. Postnatal surfactant and prolonged use of indomethacin in severely preterm neonates have been thought to have a contributory role in reducing white matter injury. Surfactant administered prophylactically or as rescue therapy with ventilator support is proven to reduce risk of RDS.

Mechanical ventilation (MV) is hypothetically essential in efforts to reduce brain hypoxia especially in ELBW with respiratory distress. It is, however, interesting to note that increased duration of conventional MV is associated with increased risk of CP. The positive intrathoracic pressure created impedes venous return and cardiac output, causes the cerebral blood flow to fluctuate. Changes in ventilator practice and avoidance of hypocapnia may decrease the rate of cystic periventricular leukomalacia.61

Magnesium sulphate (MgSO4) infusion to mothers used for neuroprotection of the preterm fetuses has been favorably reviewed with no severe deleterious effect, substantial reduction of risk of CP (RR 0.68, 95% CI, 0.54–0.87) and also significant reduction in relative risk of substantial gross motor dysfunction (RR 0.61; 95% CI, 0.44–0.85).62 However, it was not found to statistically improve pediatric mortality (RR 1.04; 95% CI, 0.92–1.17), or other neurological impairments or disabilities in the first few years of life. Most clinical trials suggest administration of MgSO4 intravenously with loading dose of 4 to 6 gm and maintenance doses which vary from none to 2 gm per hour. The gestation of pregnancies at risk randomized for the treatment also varied from between severely premature infants below 30 weeks and those less than 33 weeks.63,64 It is advised that MgSO4 be administered to pregnancies below 32 weeks of gestation in an anticipation of premature birth.55,66 Should MgSO4 be used as a measure to reduce risk of CP, guidelines on the appropriate dosage, route of administration and the gestational week for initiation of therapy need to be formulated to achieve optimum effects for the fetus and mother. Doses may have to be varied especially in overweight women. Further randomized clinical trials are, therefore, required.
Head Cooling in Neonates with Hypoxic Ischemic Encephalopathy

It has been shown that reducing temperature of 2°C for 72 hours for neonates diagnosed with hypoxic ischemic encephalopathy (HIE) within 6 hours after delivery will reduce rate of mortality or major neurodevelopmental disability (RR of 0.7) with no major adverse effect. The recommendation seems to be beneficial in term and late preterm newborns. Nevertheless, more trials to refine the intervention is required to ascertain the duration, selection of cases, technique of cooling, etc.

MANAGEMENT OF CEREBRAL PALSY

After establishing a diagnosis, management involves a multidisciplinary approach for optimal result. The multidisciplinary team would provide physical therapy, occupational therapy, speech therapy, orthotics, nutrition, social work, orthopedics corrective surgery, and general pediatric care for holistic management. Specific clinical management could be:

Nonsurgical Management

Some of the commonly used medications are directed to managing spasticity. Three common medications used are diazepam, baclofen, and dantrolene. Diazepam works centrally by increasing the release of neurotransmitter chemical called gamma-aminobutyric acid (GABA), which can calm the muscle. Baclofen which is also a muscle relaxant works at the spinal cord level, binding to GABA receptors. This will decrease the signaling pathways from spinal cord to skeletal muscles. Dantrolene can be given orally or intrathecally. Dantrolene works by decreasing the release of calcium in skeletal muscles leading to decrease excitability. Botulinum toxin is frequently used to decrease contractions and stiffness by blocking the release of neurotransmitted acetylcholine inhibiting muscle contractions.

Other than drug therapy, physical therapy is an important component for CP patient as it can improve the strength of muscle preventing contractions. Bracing can prevent deformity or slow the progression of deformity.

It is also believed that stem cell therapy might be able to replace lost oligodendrocytes from hypoxic-ischemic event. This strategy may lessen the motor impairment suffered by CP patients. Research on stem cells in animals had shown positive results. Research is undergoing for stem cell therapy for CP in humans. Four on-going trials, two in US, one in Korea and one in Mexico, are looking at safety and effectiveness of stem cell therapy in CP. All the clinical trials are still incomplete.

Hyperbaric oxygen was thought to be able to improve CP by giving highly concentrated oxygen into the body greater than atmospheric pressure. This is not approved by Food and Drug Administration (FDA), US as several studies report no benefit. Counseling of care provider is also an integral part of the management for CP. Parents of CP patients should be made aware of the availability of CP support groups. They should be given opportunities to ask questions and have their concerns addressed. Clinicians have the responsibility to lessen parents’ guilt and resolve their inner conflicts so as to accept their children with positive approaches to further care.

Surgical Interventions

Surgery is usually considered when patient has deformity that decreases function, to alleviate pain or improve the activity of the daily living. Surgical procedures, such as lengthening of muscles and release of limb muscles and tendons that cause contractures are commonly done.

Selective dorsal rhizotomy (SDR) is a procedure that selectively divides portions of the dorsal lumbar sacral roots of the spinal cord, interrupting the spinal reflex arc on the sensory side leading to reduction in spasticity without causing paralysis. A meta-analysis of three randomized clinical trials for SDR in CP confirms that SDR consistently reduces or eliminates spasticity.

Chronic cerebellar stimulation to reduce seizures in CP patient is controversial. In this approach, constant stimulation therapy works by implantation of a controlled-current stimulator applied intermittently to the superior-medial cerebellar cortex. Some research did show reduction in seizure activity after a 17-year follow-up. Results of such intervention need to be interpreted with caution as objective evaluation is difficult due to the nature of the disease.

PROGNOSIS

Due to the heterogeneity of this disease, the prognosis varies. Most patients live to be adults especially those with less severe functional disabilities. In a UK analysis, the prognosis for children with CP is better than for those with more severe disabilities. It is important to note that the prognosis for children with CP is better than for those with more severe disabilities.
of children with CP, 20-year survival rate ranged from 87 to 94%. There are many contributing factors to diminished life expectancy in CP patients which include mental retardation, severe language disability, severe physical disability, severity of seizures and tube feeding, etc.76

CONCLUSION

Cerebral palsy is a lifelong challenging condition for patients and care providers. Each patient needs individual treatment tailored to the type and severity of disabilities. The high cost of managing may render suboptimal supportive care affecting the long-term outcome of CP patients.

Litigation and legal suits will prevail if common clinical pathways in managing preterm and ‘asphyxia’ associated with CP are not established. Criteria for a causal relation established by the American College of Obstetricians and Gynecology and documentation of counseling points delivered to the pregnant mother with high fever, infection, preterm labor and intrapartum ‘fetal distress’ birth would assist in avoiding such litigation in CP related to intrapartum events.

Despite an increasing highlight on the possible antenatal and postnatal antecedents of CP and attempts to improve preventive measures, the prevalence remains constant for the last 40 to 50 years. In many parts of the developing world, emphasis and focus on improved ante, intra and postpartum care are much needed to avoid litigation and ensure high quality healthcare output.

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