INTERNATIONAL CORNER

NEONATAL ENCEPHALOPATHY AND CEREBRAL PALSY: A REVIEW OF THE PAST HOPE FOR THE FUTURE

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INTRODUCTION

Improvements in obstetrics managements and neonatal care have led to marked decreases in maternal and perinatal mortality and to sharp declines in physical trauma to the fetus during birth. On the other hand, the increased use of electronic fetal monitoring and cesarean section have had minimal or no effect on the occurrence of fetal and neonatal neurological morbidity specially neonatal encephalopathy and cerebral palsy.

Definitions

Cerebral palsy (CP) is a group of non progressive conditions that result from an insult to developing central nervous system, which can occur in the uterus, during delivery or during the first 2 years of life. The definitive diagnosis of CP is usually made at age 2 to 3 years (1). The characteristic signs are abnormal control of movement or posture, muscle weakness, ataxia, and rigidity. The condition is frequently accompanied by sensory impairment, and cognitive limitation. Clinical findings depend on the extent and location of the CNS damage. The severity ranges from mild motor impairment to whole body involvement. Clinical patterns of involvement include: diplegia (leg involvement with little effect on the arms); hemiplegia (involvement of the ipsilateral arm and leg), quadriplegia (all four limbs are involved). Coexistent movement disorders can be spasticity, rigidity, hypotonia, dystonia or a mixture of these disorders (2). The overall reported prevalence of CP has remained stable at about 2 to 3 per 1000 live births and there has been no consistent decrease in its frequency over the past two decades (3-8).
Neonatal encephalopathy (NE) is a clinically defined syndrome of disturbed neurological function in the earliest days of life in term infants, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes (9). Until now there is no universally agreed and accepted definition of neonatal encephalopathy in general clinical or research use. Many terms have been used to define this condition such as: asphyxia neonatorum, hypoxia-ischemia, fetal distress, fetal asphyxia, birth asphyxia, newborn asphyxia, perinatal asphyxia, neonatal asphyxia, hypoxic-ischemic encephalopathy, newborn encephalopathy, perinatal encephalopathy, neonatal encephalopathy, infant encephalopathy. Most of these terms presume intrapartum asphyxia as a common etiological denominator. Many cases of NE do not result in CP. The prevalence of NE varies among studies, depending on the definition used and the population studied. The range varies from 1.8 to 7.7 per 1000 term live births (3, 9-11).

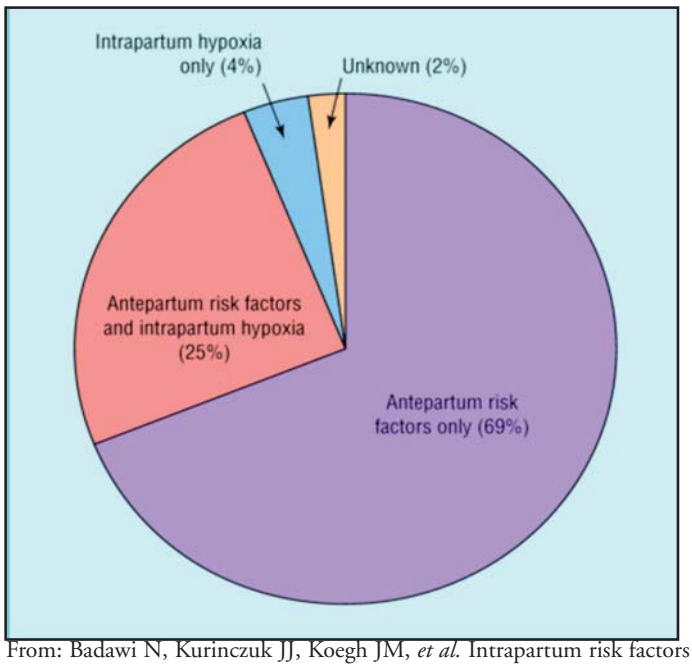
Etiology

The causes of NE and CP are heterogeneous, and many causal pathways start either preconceptionally, antepartum or intrapartum. Until recently these adverse neurological outcomes have been assumed to be the effect of "birth asphyxia". Consequently "fetal distress", "birth asphyxia" and "hypoxic ischemic encephalopathy" have been, and unfortunately frequently are still now viewed as synonymous of NE in clinical practice.
The "intrapartum asphyxia theory" dates back to the late 1800's when W. J. Little, a London orthopaedic surgeon, first proposed the association of the conditions, known today as cerebral palsy, with events complicating the perinatal period: "premature birth, difficult labours, mechanical injuries during parturition to head and neck, where life had been saved, convulsion following the act of birth, were apt to be succeeded by a determinate affection of limbs of newborn children, spastic rigidity, from asphyxia neonatorum and assimilated it to the trismus nascentium and the universal spastic rigidity sometimes produced at later periods of existence" (12).
Actually, Little's disease, spastic diplegia, is not now believed to result from intrapartum events. The term "cerebral palsy" was coined in 1888 by W. Osler (13) who also noted the association of this disorder with difficult deliveries and asphyxia requiring prolonged resuscitations in the newborn. Sigmund Freud in 1890 (14) was the first to argue that perinatal asphyxia might be a marker of prior fetal compromise associated with adverse events long before labor and delivery.
However, the asphyxia theory regained emphasis after experiments in primates demonstrated that perinatal asphyxia could cause brain damage (15, 16). This model led to a widespread perception among clinicians and public that cerebral palsy in term babies is due to preventable intrapartum hypoxia, therefore all adverse neurological outcome are today central in obstetric litigation. This misunderstanding has contributed to the escalation of cesarean section rate and has had further devastating effects. In fact this pervasive belief has prevented the carrying out of research focusing on alternative and more important causal pathways for NE and CP. It is clear that at present our understanding of factors that may cause neurological injuries during pregnancy and labor is, at best, incomplete.
Historically the term "hypoxic ischemic encephalopathy" (HIE) arose on the assumption that the majority of newborn brain injuries do occur during labor and delivery due exclusively to "intrapartum asphyxia". The acquisition that asphyxia/hypoxia can cause (and in some cases it does) brain damage during birth or labor, has led to the generalization of this

one known causal pathway on the etiology of all cases of NE. Over the past two decades a growing body of indirect and direct evidences led to the conclusion that this view is no longer tenable.

Looking specially at the intrapartum period, Badawi and colleagues (10, 11) in the Western Australian case-control study, observed that there was no evidence of intrapartum hypoxia in over 70% of cases of NE. They further observed that pure intrapartum hypoxia accounted for only 4.9 % of moderate or severe newborn encephalopathy and that in 25 % of cases, intrapartum events may be superimposed on preconceptional or

Fig. 1 – Distribution of risk factors for newborn encephalopathy



From: Badawi N, Kurinczuk JJ, Koegh JM, *et al.* Intrapartum risk factors for newborn encephalopathy:
The Western Australian case-control study. *BMJ 1998; 317:1554.*

antepartum preexisting insults (17).

However, at present it is very difficult, and often impossible, to determine the cause and the precise time when a brain damage has occurred. This issue often arises in medicolegal proceedings but "professional" ideas in this context are often simplistic.

Most clinical evaluations of birth asphyxia rely on a cluster of fetal or neonatal signs that are not specific (17). The markers currently used to diagnose intrapartum hypoxia, such as meconium stained amniotic fluid, low Apgar score, abnormal cardiotocography, fetal and neonatal acid/base status, etc all are aspecific and lack both sensitivity and specificity (9, 18, 19).They must be considered effects rather than cause of fetal injury. Moreover, given the frequency with which these markers are present in newborns with normal outcomes, it is unreasonable to assume that their presence in an infant who later develops encephalopathy is evidence of causation. Surprisingly, however, this simplistic assumption has found a pivotal place in day-to-day medical thinking and medicolegal proceedings.

Contribution of intrapartum events

In 1997 (data were published in 1999) (18) an International Cerebral Palsy Task Force was set up in order to define a causal relation between acute intrapartum events and cerebral palsy. This was a multidisciplinary group including obstetricians, neonatologists, neurologists, and other clinicians and scientists.

Moreover, they made the following statements:

- the terms "fetal distress" and "birth asphyxia" are inappropriate and should not be used clinically;
- in the clinical context fetal asphyxia is a progressive hypoxemia and hypercapnia with a significant metabolic acidemia (20,21). In practice, the timing of the onset and progression of these changes can be difficult or impossible to ascertain;
- the term "hypoxic ischemic encephalopathy" should not be used, as hypoxia and ischemia have often not been proved and have been assumed from a variety of clinical markers that do not accurately reflect hypoxia and ischemia of either acute or chronic origin;
- over 75% of cases of neonatal encephalopathy have no clinical signs of intrapartum hypoxia;
- if hypoxia and ischemia have not been proved the correct diagnosis should be neonatal encephalopathy (NE);
- when metabolic acidemia has been conclusively proved by fetal blood gases and umbilical cord arterial or very early neonatal blood gases, or both, it remains to be proved whether this is attributable to a chronic or intermittent hypoxia of longstanding duration, days or weeks, or whether to a de novo acute hypoxia occurred during labour or birth in a previously healthy fetus;
- reduced variability of the fetal heart rate, meconium staining amniotic fluid, low Apgar score, and neonatal encephalopathy may all represent the first recognised signs of a chronic neurological compromise. In a chronically compromised case, the intrapartum signs may precipitate an obstetric intervention such an instrumental or cesarean delivery in the hope that the pathology is of recent onset and still reversible. Retrospectively the presence of these signs and the decision of carers to act to prevent possible acute compromise may mistakenly be taken as evidence of acute compromise.

They also suggested criteria to define an acute intrapartum hypoxic event. These criteria were updated in 2003 by the ACOG Task Force on Neonatal Encephalopathy and Cerebral Palsy, in conjunction with the American Academy of Pediatrics (22), as follows:

Essential criteria (must meet all 4):

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 of severe or moderate neonatal encephalopathy in infants born at >/= 34 weeks gestation
3. Cerebral palsy of the spastic quadriplegia or dyskinetic type
4. Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, i.e. 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

The report confirms what before established by the International Task Force and emphasizes that the historical factors used to define perinatal

asphyxia (ie, meconium, Apgar scores) are not specific to the disease process leading to the neurologic damage. Using these nonspecific markers incorrectly identifies individuals as being exposed to "perinatal asphyxia".

Other statements in the report are:

- while neonatal encephalopathy does not always lead to permanent neurologic impairment, the pathway from an intrapartum hypoxic ischemic injury to subsequent cerebral palsy must progress through neonatal encephalopathy;
- only cerebral palsy involving spastic quadriplegia is associated with an acute interruption of the blood supply; purely dyskinetic or ataxic cerebral palsy generally is genetic in origin.

Moreover it has been defined that neonatal encephalopathy of any etiology occurs in approximately 2-8 births per 1000 term infants. HIE is only a small subset of the causes of NE in fact approximately 9 % of cases of cerebral palsy are due to possible birth asphyxia**.** The best available evidence suggests an incidence rate for pure HIE (hypoxic ischemic encephalopathy) (ie, neonatal encephalopathy with intrapartum hypoxia in the absence of any other abnormality) of approximately 1.6 per 10,000 births. Most infants with mild to moderate neonatal encephalopathy develop normally (3, 7, 18, 22). Most infants thought to have birth asphyxia do not develop motor or cognitive disabilities unless the event was severe and prolonged.

Both task forces provide sound arguments that cerebral palsy has many causes, including developmental and metabolic abnormalities, infection, autoimmune and coagulation disorders, as well as trauma and hypoxia in the fetus or neonate.

Comments on proposed criteria

Both task forces have provided objective evidence that antenatal causes of brain injuries are now felt to be more important than perinatal or neonatal causes and that the old hypothesis of "birth asphyxia" as unique pathway to cerebral palsy, cannot be supported any longer.
On the other hand as at present specific tools to define the causes and the time of fetal injury are still lacking, the presence of essential criteria cannot be considered to birth asphyxia, therefore there are possible misuses of the statements especially if a case is subject to a lawsuit.
With this regard, both task forces well explain in the reports further pivotal specifications:

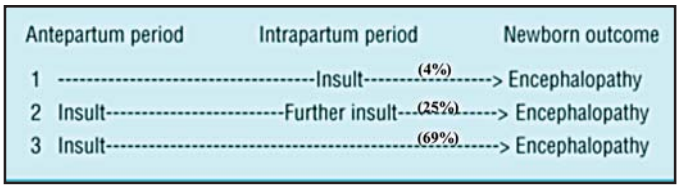
- most babies with a fetal/early neonatal metabolic acidosis will not have cerebral palsy, but after a severe damaging intrapartum hypoxic event, metabolic acidosis will be present;
- many babies with neonatal encephalopathy will not have cerebral palsy, but after a severe damaging intrapartum hypoxic event, there will be evidence of neonatal neurological abnormality;
- most children with spastic or dyskinetic cerebral palsy do not have a history of 'fetal distress', but after a severe damaging intrapartum hypoxic event, there will be signs of global neurological damage;
- most other etiologies, such as coagulation disorders, infectious conditions, or genetic disorders, are not always identifiable during pregnancy in the mother or in the fetus.

Consequently without a 'gold standard' measure of intrapartum hypoxia, it is not possible to assess the sensitivity and specificity of the above criteria as markers of a damaging acute intrapartum hypoxic event. In other words: if all criteria are not present an intrapartum hypoxic event must be excluded; if all criteria are present it is possible that an intrapartum hypoxic event has occurred but it does not mean that it has really occurred.
It is necessary that all the criteria are present to confirm that an intrapartum hypoxic event has occurred, but their presence is not sufficient to state that such an event has really occurred, because the clinical findings at birth may be the first recognized signs of a chronic neurological compromise of antenatal origin.

The assumption of intrapartum asphyxia

Animal studies provided objective evidence of the relationship between total and chronic asphyxia and brain damage (16). The degree of hypoxia that is necessary to produce permanent brain damage is close to that which is lethal (23). In humans most infants thought to have acute birth asphyxia do not develop neurologic disabilities unless the event was severe and prolonged. In fact, many physiological mechanisms protect the fetus from acute hypoxia, allowing it to survive intact for a longer period than an adult in similar conditions (24). Many circulatory responses and non circulatory factors contribute to neuronal preservation. Even with severe and prolonged asphyxia, most newborns recover with minimal or no neurologic sequelae.
The markers currently used to diagnose intrapartum hypoxia (low Apgar score, abnormal cardiotocography, fetal and neonatal acid/base status) are widely aspecific. They relate to a depressed newborn (the effect) rather than to a causal pathway. Thus, we should not be surprised that, using these non specific markers as part of the recruitment criteria to diagnose birth asphyxia, we will always find an association between these markers and "hypoxic ischemic encephalopathy". Moreover, abnormality on these markers at birth is insufficient to demonstrate whether the injury has occurred during pregnancy or birth. In fact, while some injuries can occur intrapartum in a previously normal baby, many others may have started months or weeks before and neonatal symptoms at

Fig. 2 – Possible pathways leading to encephalopathy



From: Badawi N, Kurinczuk JJ, Koegh JM, *et al.* Intrapartum risk factors for newborn encephalopathy:
The Western Australian case-control study. *BMJ 1998; 317:1554.*

birth simply reflect a previous neurological compromise.
The Apgar score, was originally designed in 1952 by Virginia Apgar as a quick method to assess the clinical status of the newborn and the effectiveness of resuscitation (25-27). Over the years, however, it covered a much broader role in many studies in prediction of neurologic outcome in the newborn. Its misuse has led to an erroneous definition of asphyxia. Although there was little scientific evidence to support the use of the Apgar score in this way, such a validity was widely assumed even within the medical community. Based on the assumption that most childhood neurologic disorders were due to intrapartum hypoxia, attempts were made to combine the Apgar score with umbilical acid-base assessment. The Apgar score was found to be a poor predictor of acidemia and acidemia, in turn, a poor predictor of the Apgar score; both, even taken

together, were poor predictors of subsequent neurologic outcome. In 1996, to emphasize the appropriate use of the Apgar Score, The American College of Obstetricians and Gynecologists and The American Academy of Pediatrics jointly published a statement (27). The highlights of the statement include: the Apgar Score is useful in assessing the condition of the infant at birth; the Apgar score alone should not be used as evidence that neurologic damage was caused by hypoxia or from inappropriate intrapartum treatment. In summary, a low Apgar score at birth does not by itself indicate that intrapartum asphyxia has occurred. On the other hand a rapid improvement in scores by 5 to 10 minutes indicates a low risk to subsequent neurological disability.

The electronic fetal monitoring

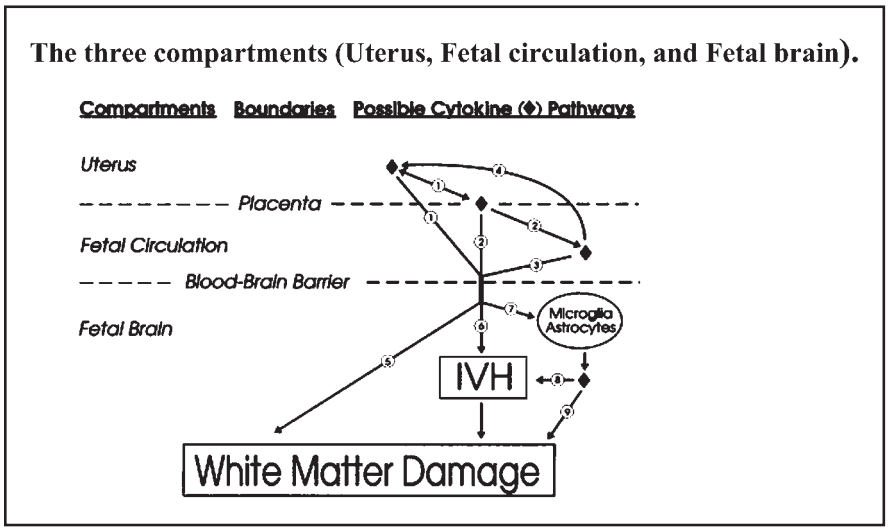
Electronic fetal monitoring (EFM) was introduced in the 1960s with the idea that changes in fetal heart rate pattern would identify hypoxia in time to prevent perinatal brain damage, thereby reducing the incidence of neurological morbidity including cerebral palsy. Several decades later it has been evident that this hope has not been realized. In fact, in spite of widespread use of intrapartum fetal monitoring, the rate of cesarean section performed for diagnosis of "fetal distress" derived from EFM has increased while cerebral palsy prevalence has remained stable at about 2 to 3 per 1000, identical to, or higher than, that seen in countries where the availability of emergency cesarean delivery and EFM is lacking (7). A number of systematic reviews of randomized controlled trials do not support the routine use of intrapartum EFM. Compared with intermittent auscultation, EFM does not reduce the rate of perinatal deaths or the number of newborns admitted to neonatal intensive care. Moreover, EFM was found to result in higher rates of cesarean section and operative deliveries (28, 29). In 1996 the U.S. Preventive Services Task Force states that "routine EFM for low-risk women in labor is not recommended"(30). For high-risk women, the task force states, "There is insufficient evidence to recommend for or against EFM..." The Canadian Task Force on the Periodic Health Examination made a similar recommendation (31). A technical bulletin from the American College of Obstetricians and Gynecologists states that either EFM or intermittent auscultation is acceptable and acknowledges the risk of increased interventions with continuous monitoring (29).

The positive predictive value of an abnormal EFM is very low (1.2 %) (32-33) and the false positive rate extremely high (99.8 %) (34).Intervention on the basis of the fetal heart rate does not improve outcomes which are the same regardless of whether "fetal distress" is managed operatively or conservatively. In fact the vast majority of babies with an abnormal EFM will have a normal outcome. On the other hand, findings upon arrival at the hospital may reflect a potentially long-standing preexisting neurological insult refractory to obstetrical intervention. This lack of specificity of the EFM has made it a very contentious tool both in clinical and legal practice. Even in controlled research setting with expert clinicians, the interpretation of an EFM tracing have shown very poor interobserver reliability (35, 36). In one study, (37) reviewers were given two identical tracings and antenatal histories but were told that the outcome was good in one case and poor in the other. When the outcome was told as poor, the reviewers were more likely to find abnormalities in the tracing and to disagree with the management. Moreover, the same observer (38) given 100 abnormal tracings, would be unlikely to be able to pick out the one that was associated with a bad outcome as there are no classical features of such a tracing. These studies demonstrate the danger of retrospective reviews of fetal heart rate tracings mainly in legal practice.

On this subject Clark and Hankins (7) note: "If our best evidences no longer recommend EFM, why is it still so widely used? A test leading to an unnecessary major abdominal operation in more than 99.5 % of cases, should be regarded by the medical community as absurd at best. Given such considerations, one must conclude that operative intervention based on electronic fetal heart rate monitoring has probably done more harm than good and has probably costed more in terms of maternal morbidity and mortality over the past 30 years than it has benefitted babies".

It does not seem simple to change a technology used for such a long time in clinical practice. There are educational, technical, financial and chiefly legal barriers. Probably the fear of lawsuits is now the main factor that contributes to maintain a technology that has totally failed to live up to its promise. The task of the scientific community is now that of making clear the actual validity of EFM and that of carrying out alternative more reliable tools.

Fig. 3 - Pathways of possible white matter damage.



The placenta represents the boundary between the mother and fetus
The fetus' BBB represents the boundary between the systemic circulation and the brain
From: Dammann O, Leviton A. The role of perinatal brain damage in developmental disabilities: an epidemiologic perspective. *Mental Retard Dev Disabil Res Rev* 1997; 3:13 .

Fetal acidosis

Fetal scalp, umbilical arterial cord or very early neonatal blood gases (less than 1 hour) are believed to be the best measure of the degree of an intrapartum hypoxic event. Respiratory acidosis at delivery does not lead to neurologic complications (39, 40). Furthermore, there is little correlation between severe acidosis with neurological status in the neonatal period (41, 42). Metabolic acidosis has been associated with an increasing risk of neurological and systemic complications (43-45), but the incidence of neurological complications is increased significantly only with an umbilical arterial pH below 7.00 and a base deficit of more than 16 mmol/l (46, 47).

The technique for measuring blood gases is critical (48). In the umbilical cord, only the arterial blood must be collected by skilful staff. However, if records of both arterial and venous umbilical cord gases exist, the difference in partial pressure of CO2 of more than 25 mmHg suggests an acute rather than chronic acidosis (49).

Several factors limit the usefulness of acidemia

in determining the timing of a neurologic insult. Not all newborns with metabolic acidosis will develop neurologic abnormalities. A metabolic acidemia at delivery only represents the degree of the insult, not the duration of acidemia nor the moment of the initial event. Assessment of the metabolic acidosis at birth is most useful for its negative predictive value (50). In other words: a normal cord arterial pH (>7.20) provide compelling evidence that significant intrapartum asphyxia has not occurred; the presence of metabolic acidosis at delivery does not cut out preexisting neurologic abnormalities of antepartum origin. Clinical cordocentesis studies have confirmed the presence of antepartum acidosis (51, 52). When metabolic acidemia has been detected, it remains to be proved whether an acute hypoxic event has occurred during labour in a previously healthy fetus or whether this is attributable to a chronic or intermittent hypoxia of longstanding duration. Furthermore neonatal acidemia may reflect a neonatal exposure to asphyxia attributable to postpartum causes (i.e. difficult resuscitation, respiratory distress, neurologic injuries due to other causes) rather than an intrapartum insult.

NEONATAL IMAGING

Improving technology and increasing data regarding morphological changes and evolution of fetal and neonatal brain injuries have made neuroimaging techniques helpful tools in determining the time and the severity of the injury.

To this end, we have to consider both the time that is required before morphological changes become apparent and the pathological patterns that relate to the clinical evolution of the brain damage during that time.

- Infants who die immediately following an acute asphyxial event have structurally normal brains because changes have not had time to occur (16).
- It is required more than 18 hours before morphological changes become apparent. After an acute cerebral insult, oedema appears within 6-12 hours and clears by 4 days after the insult (18).
- Cystic lesions develop over 10 to 14 days (53,54).
- Early detection (within 6-12 hours) of cerebral oedema with or without intracerebral haemorrhage, or detection of cystic lesions within 10-14 days after birth suggest an antenatal injury.

Therefore, in trying to date fetal brain damage, information cannot be achieved from belated imaging studies (weeks or months after delivery). Brain imaging can be indicative of an approximate window, rather than determine the precise moment when the injury occurred.

Ultrasonography is widely used in neonatology. About 50 % of infants who have echolucent zones in the periventricular white matter or ventriculomegaly on neonatal cranial ultrasound scans subsequently develop cerebral palsy (55).

The main limitations of this technique include subjective interpretation of altered echogenicity, difficulty in distinguishing hemorrhagic injuries, subobtimal visualization of the subarachnoid space, posterior fossa and cerebral cortex. The ultrasound tends to underestimate cortical damage. This later is an important limitation because cortex injuries are the most frequent lesions in the term fetus. Lesions may take 2-3 days to develop. Additionally, in the newborn at term, even early performed, cranial ultrasound scans poor correlate with outcome (56,57).

Computed tomography (CT), can provide good anatomic detail and helps define the site and the extent of the lesion. It can visualize the ventricular size and periventricular abnormalities characteristic of PVL. Pathological CT scans correlate strongly with poor outcomes. Abnormalities include haemorrhages and hypodensities. Hypodensities may take 10-14 days to develop (50).

Magnetic resonance (MRI) relates to the tissue composition and metabolic activities. It can evaluate the process of myelination and the gliotic reaction in the brain and can help to determine the trimester in which fetal brain damage has occurred. MRI seems to be more sensitive than computed tomography for the detection of subtle brain injuries predictive of outcomes (58). Recent MRI reports have described various patterns of brain lesions in infants with encephalopathy and attempted to correlate the lesions with clinical data to suggest the etiology and timing of the brain lesions. In 2003 Cowan et al (59) reported findings from two centers in the UK and Netherlands in a total series of 351 infants selected on the basis of "clinical signs that were likely to be a result of difficulties that arose during birth". They concluded that "90 % of term infants with neonatal encephalopathy, seizures, or both, but without specific syndromes or major congenital defects, had evidence of perinatally acquired insults, and there was a very low rate of established brain injury acquired before birth." In fact, only 1 % had evidence of old lesions on imaging or autopsy.

These findings demonstrate the power of MRI in determining the site and the extent of the brain damage, in evaluating the evolution of the injury and leading the therapeutic approach but they cannot be regarded as referral patterns of hypoxic ischemic encephalopathy nor as evidence of intrapartum hypoxia/ischemia.

In fact the aim to test the relative contribution of intrapartum asphyxia versus antenatal causes of encephalopathy could not be reached by this study because of many design limits. Cowan and colleagues split their patients into two groups. The first group consisted of infants with signs of encephalopathy (abnormal tone pattern, feeding difficulties, altered alertness) with or without seizures and, with a view to strictly select the cases of hypoxic ischemic encephalopathy the authors added to the previous at least three of the following criteria: late decelerations on fetal monitoring or meconium staining; delayed onset of respiration; arterial cord blood pH less than 7.1; Apgar score less than 7 at 5 min; and multiorgan failure. The second group consisted of infants with seizures but none of the above signs.

It is well known that none of the above criteria are specific for hypoxic ischemic encephalopathy. At best they can be interpreted as suggestive of a depressed state at birth but cannot be considered as confirmatory of a causal intrapartum hypoxia/ischemia. Moreover those are arbitrary criteria that do not relate to those now admitted by scientific organisms (International Cerebral Palsy Task Force 1997); ACOG Task Force on Neonatal Ecephalopathy and Cerebral Palsy (2003). Finally, as explained above, if the criteria are not present an intrapartum hypoxic event must be excluded, if the criteria are present it is possible that an intrapartum hypoxic event has occurred but it does not mean that it has really occurred. On the other hand, it is not clear why infants with seizures have been kept distinct. If the aim was to separate infants with encephalopathy from infants without encephalopathy, we have to remember that seizures are signs of encephalopathy; if the aim was to separate infants with hypoxic ischemic encephalopathy from infants with encephalopathy from other origin, we have to remember that the presence of the selected criteria cannot be considered evidence of intrapartum hypoxia/ischemia as well as the presence of seizures does not exclude an intrapartum hypoxic event.

Using these nonspecific markers of hypoxia as part of the recruitment criteria, the study was predestined to find an association between these signs and hypoxic encephalopathy and over-estimate the intrapartum contribution. Therefore these findings cannot be regarded as referral patterns of hypoxic ischemic encephalopathy._

With respect to the timing of the injury, considering the morphological evolutions of the pathological patterns of the brain damage during the

time, brain imaging cannot determine the precise moment when the injury occurred, but it can be indicative of an approximate window (2-3 days to 2 weeks) which widely includes the length of the delivery (6 – 12 hours). Therefore, such a precise timing often can only be presumptive.

Placental pathology

Until recently, placental pathology has met a low interest among both pathologists and obstetricians. It has only been because of the rise in obstetrical litigation that placental examination regained emphasis in the attempt to link clinical correlations of children with cerebral palsy to the pathology of their placentas (60). After birth, the placenta is an easily accessible and very significant representative part of the original placental-fetal unit. Placental pathology may represent the cause, the effect or an associated finding of the pathological process occurred in mother or in the fetus. Accurately defining the pattern of specific placental lesions, we can often assess the causes (maternal, fetal or both), the timing and the pathological pathway of the fetal or neonatal brain injury.

Placental evaluation indicates a remarkable increase in severe fetal chorioamnionitis in placentas of infants who developed neurologic impairment (61). Histologic chorioamnionitis and other placental infections demonstrated by placental examination, are strong predictors of fetal brain damage. Histologic chorioamnionitis must be considered a definite intrauterine fetal infection which frequently occurs without maternal or fetal symptoms.

Placental markers of thrombotic disorders were associated with, intrauterine growth retardation, neurologic injury and possibly underlying inherited thrombophilia (61). In 1995 Redline and Pappin (62) proposed the term "fetal thrombotic vasculopathy" (FTV), a pattern of thrombi in the fetal circulation of the placenta which has been associated with serious brain injuries. Correlations have been found between FTV and intrapartum death, stillbirth, fetal cerebral thrombi or infarcts. Placental FTV is evidence that thrombi have occurred in the fetal circulation before delivery. A very significant proportion of stillborns or neonates with FTV who die in the perinatal period have somatic thrombi in the brain, kidneys, lung. Placental FTV, as well as other fetal or maternal conditions have been linked to fetal or perinatal stroke (63).

Specific placental features are also present in most maternal and fetal diseases.

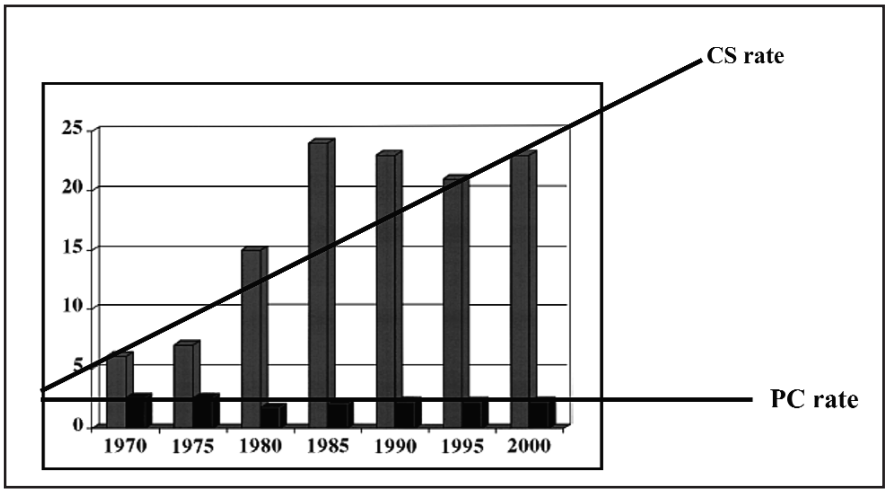
RISK FATORS AND PATHOGENESIS

Intrauterine infections (IUI) (maternal or placental), other than TORCH infections, lead to an increased risk for cerebral palsy both in term and in preterm infants (64). Periventricular leukomalacia is the most severe and frequent cause of cerebral palsy in preterm delivered children. Until recently these lesions have been considered of hypoxic-ischemic origin, resulting from impaired perfusion at the vascular border zones between major cerebral arteries where perfusion pressure is least. Therefore, these periventricular zones are the most susceptible to a decrease in cerebral blood flow. Chorioamnionitis has a remarkable risk for the development of cerebral palsy (6). Both in term and preterm newborns, adverse outcomes correlate well with histopathologic demonstration of chorioamnionitis or funisitis in the placenta, and poorly with symptomatic infections. Fever, maternal leukocytosis, uterine tenderness, purulent vaginal discharge are more usually the result of deciduitis that often is not associated with chorioamnionitis. Severe chorioamnionitis with fetal injury frequently occurs wthout maternal symptoms. The mechanism by which intrauterine infections may be linked with neonatal neurologic morbidity may be direct (related to cytotoxic effect of bacterial toxins (65) or indirect (related to the immune response).

Cytokines are a normal component of the immune response as well as cellular mediators of the fetal inflammatory response. The proinflammatory cytokines IL-1, IL-6 and TNF-alpha might be the link between prenatal intrauterine infection and neonatal brain damage. The mother, fetus, placental villi, chorion, and umbilical vessels all produce cytokines as part of the inflammatory response to infection (66). The fetal response to infection and inflammation is analogous to the adult systemic inflammatory response, which occurs during sepsis (67). Intrauterine exposure to infection causes fetal production of cytokines which leads to reduced fetal perfusion by causing fetal hypotension, vasoconstriction of the umbilical cord vessels, or by inducing disseminated intravascular coagulation with cerebral arteriolar obstruction and multiorgan system dysfunction. The subsequent decreased perfusion in vulnerable regions of the fetal brain can result in necrotic foci from impaired perfusion (ischemic lesions). On the other hand cytokines produced as part of the inflammatory response to infection, may have a direct toxic effect on oligodendrocytes and myelin leading to white matter damage (non ischemic lesions) (16).

The presence of cytokines in the three relevant maternal/fetal compartments (uterus, fetal circulation, and fetal brain) and the ability of the cytokines to cross boundaries between these compartments (placenta and blood-brain barrier), may explain the increased risk of white matter damage subsequent maternal IUI both in term and in preterm newborns (66).

Fig. 4 - Trends in Cerebral palsy and cesarean section.



From: Clark SL, Hankins GDV. Temporal and demographic trends in cerebral palsy – fact and fiction. *Am J Obstet Gynecol 2003; 188:628.*

Histopathological demonstration of chorioamnionitis in the placenta and increased cord blood of IL-6 levels are strong predictors of fetal morbidity. The presence of funisitis is evidence of a systemic fetal inflammatory response. Genetic factors may be relevant to maternal and

fetal responses to infection (67, 68). Known genes coding for inflammatory cytokines influence the level of production of the cytokines and the magnitude of the inflammatory response. Human studies support a strong genetic component associated with mortality from infectious causes (69). The end result of infection and inflammation is revealed by damage from reactive oxygen species. In patients with intrauterine infection, elevated levels of lipoxygenase and cyclooxygenase pathway products can be demonstrated in maternal serum, fetal serum, and amniotic fluid. There are also increased concentrations of cytokines (IL-6 and TNF-alpha) in the serum and amniotic fluid of such women, which may predate the development of clinical chorio-amnionitis by weeks or even months (70). These pro-inflammatory cytokines could decrease the production of neurotrophic and neuroprotective factors such as NGF and BDNF and increase the production of NO, VEGF and PGE. These factors increase apoptosis and also may lead to angiogenesis defects neurological diseases and/or cognitive defects (71,72). In addition other mechanism such as increased maternal temperature, placental endothelial damage and increased coagulation tendency, fetal hypoxia or acidosis, and fetal hypotension may also aggravate fetal brain damage. Intrauterine infection may be established very early in pregnancy and may remain clinically unrecognized.

Animal models support the hypothesis that viral infections also could result in brain damage Maternal infection with pestiviruses led to dysmyelination in lambs and cystic changes in the developing periventricular white matter of lamb fetuses (73).

Noninfectious causes of inflammation may also play roles in fetal brain damage.

Maternal coagulation disorders

In addition to infection and inflammation, maternal coagulation disorders, such as factor V Leiden mutation and deficiencies of antithrombin III and protein C and S, may predispose the fetus to cerebral palsy. Maternal thrombophilia including maternal deep vein thromboses promote intraplacental clotting. Pregnancy itself is a risk factor (74). Leviton and Damman (75) suggested that increased circulating levels of activated coagulation factors enhance the influence of inflammation factors, which in turn can promote coagulation. Activated coagulation factors in newborns with systemic inflammatory response may contribute to the occurrence of cerebral white matter damage by exacerbating inflammatory phenomena. The inflammatory and coagulation pathways are mutually interactive. Thrombotic lesions in the placenta have been found in cases of autoimmune and coagulation disorders (74, 75). Children with CP revealed high blood concentrations of inflammatory cytochines, chemokines and autoimmune or coagulation factors. The high sensitivity and specificity of these assays suggest that they could contribute to understanding etiology, pathogenesis and prognosis of most fetal and neonatal neurological insults. Moreover they could be used for clinical purposes in certain early management decisions. Unfortunately at present there are no possibility to use such assays in clinical practice nor blood archived specimens are available. The hope is that such analyses could expand in day-to-day medical practice (74).

Fetal stroke may be consequent to ischemic, thrombotic or hemorrhagic events occurring between 14 weeks of gestation and delivery (63). The diagnosis of fetal intraventricular hemorrhage and stroke became possible with the use of fetal cranial ultrasound imaging and MRI which better define the site and the extent of injury. It may represent an important cause of postnatal seizures, mental retardation and cerebral palsy. Alloimmune thrombocytopenia, anticoagulant therapy with warfarin or heparin, von Willebrand disease are the most common maternal condition associated with fetal stroke (77). Fetal coagulation disorders may predispose to prenatal or perinatal stroke. Congenital infections and fetal disorders such as pyruvate carboxylase deficiency have been associated with vasculopathy and resultant stroke (78).

Multiple Pregnancy

The incidence of CP is higher among multiple gestations than singleton births (79). This increased risk is associated with higher rate of premature deliveries and with twin-to-twin transfusion syndrome. To date there is no evidence that any intervention may reduce the risk of CP in this condition.

Birth asphyxia

Experimental studies have demonstrated close relationship between fetal and newborn asphyxia, and brain damage. Asphyxia is a condition of impaired blood gas exchange leading, if persistent, to progressive hypoxemia and hypercapnia. Transient hypoxemia and hypercapnia may not assume pathological significance. The degree and the duration of asphyxia/hypoxemia is important in the occurrence of brain damage. The degree of hypoxia that is necessary to produce permanent brain damage in the fetus is close to that which is lethal (23). On the other hand recurrent asphyxia (repeated episodes of asphyxial exposures) may be very dangerous because of their cumulative effect. The fetus may experience asphyxia without morbidity. Brain damage is the result of complex relationship between degree, duration, nature, recurrence of hypoxic event, and fetal cardiovascular compensatory response. Fetal cardiovascular compensation (increase of systemic blood pressure and cerebral blood flow) is the most important mechanism accounting for the protection of the fetal brain. However, the effectiveness of this mechanism will vary significantly from case to case independently of the magnitude and duration of the insult. Potential modulators of this threshold include inherited predispositions to neuronal injury, maternal thyroid diseases, placental pathology, fetal exposure to endotoxin and others (16). Intrauterine infections increases sensitivity to hypoxia-ischemia both by a direct effect of cytokines in the brain and by preventing the mechanism of cardiovascular compensation, in causing systemic hypotension and cerebral hypoperfusion. Significant fetal asphyxia leads to metabolic acidosis. The threshold of a metabolic acidosis in the umbilical arterial blood at delivery beyond which brain damage may occur has been pointed out as a base deficit of more than 16 mmol/l (80-82). Nonetheless, metabolic acidosis beyond the threshold may occur at delivery with normal outcome (16,18).

Since the nature of the asphyxia cannot be determined it is very difficult to know how often the fetal asphyxia identified at delivery occurred during labor. All markers of fetal acute asphyxia are aspecific. What is manifest at birth may represent the last in a series of asphyxial exposures occurred before the onset of labor. At present to accurate timing and judge on possible sequelae, clear clinical signs are required. MacLennan (18) defined them “Sentinel hypoxic events”. Such events, which seldom result in cerebral palsy, are cord prolapse and true knots, placental abruption, uterine rupture, amniotic fluid embolism, fetal exsanguination from vasa previa or fetalmaternal hemorrage. MacLennan concludes that it is only when such events are apparent or detectable that it helps to define the probable timing of the event and to determine whether its sequelae might have been preventable.

The question is not whether birth asphyxia can happen (of course it can) or whether it can cause brain damage (of course it can). The issues are: what proportion of neurological impairment in children is due to perinatal hypoxia-ischemia and how much to different causes; what are the non-asphyxial factors which can cause or contribute to unfavourable

outcomes. Current research suggests that contrary to previous beliefs, in most cases the events leading to neurological damage occur in the fetus before the onset of labor or after delivery. The perinatal asphyxia accounts for 6% to 8% of cases of cerebral palsy (83, 84). Research has opened new conceptual horizons into infection, inflammation, autoimmune diseases and clotting abnormalities. There is also a growing interest in "neural rescue therapies" which can be applied to ameliorate neurological injury. These therapies have generally been developed in models of hypoxic ischemic injuries but if hypoxia and ischemia are not the cause or are only components of the pathological mechanism, the experimental model does not work in clinical practice. It is no longer acceptable to label every neonatal encephalopathy as hypoxic-ischemic, it is time to define the pathophysiologies more precisely, to abandon deep-rooted prejudices and to reassess research towards alternative and more frequent causal pathways (85).

Other factors

Studies on maternal nutritional factors appear to be an additional promising approach. Clinical studies have shown that the duration of gestation and birth weight are significantly increased when omega-3 rich food or DHA supplements are taken during last trimester of pregnancy. Olsen et al (86) showed that the risk of preterm delivery was 4 times less in mothers who received such food supplements during pregnancy. DHA is credited to have anti-inflammatory and antithrombotic effect by reducing levels of thromboxane (TXA-2) and increasing prostacyclin (PGI-2) levels. In addition DHA may regulate immunoreactions and cytokines expression (87, 88).

CONCLUSIONS

Abnormal findings in the intrapartum and neonatal periods may be the consequence of preexisting antepartum events. Unfortunately intrapartum fetal surveillance and speedy delivery have failed to lower cerebral palsy prevalence in developed countries. Both antepartum and intrapartum tools now used to detect and timing neurological fetal injury are still particularly unhelpful.

Research about causes and pathological mechanism involved in CP is essential in developing strategies for prevention and treatment. Elucidating the multiple pathways leading to fetal brain injury will be the way forward in preventing this important clinical enigma.

More information about causes and pathogenesis of fetal brain injury is likely to come from further investigations of maternal infections, thrombotic disorders, genetic factors relevant to maternal and fetal response to infection and nutritional factors.

Future investigations of modulation of the pathological effect of proinflammatory cytokines by increased production of other cytokines with anti-inflammatory properties (such as IL-10 and TGF) may lead to a reduction of perinatal brain damage. Further etiologic studies employing the cytokine network are needed to develop strategies intended to prevent and treat intrauterine infections, to reduce the risk of very preterm delivery, to identify children most likely to benefit from new 'neural rescue therapies' re-focusing attention on alternative pathways to white matter damage.

Evidence is emerging that evaluation of a variety of coagulation or inflammation factors in fetal, maternal or neonatal blood may help clinicians to understand most causative factors for prenatal or perinatal brain injuries and consequently to develop further diagnostic and therapeutic strategies. Clinical investigations are urgently needed to make possible such analyses in clinical practice.

Systematic placental examination has the potential to shed light on poorly understood antenatal processes that may increase the risk of neurologic impairment and cerebral palsy. The placenta is a very complex organ and should deserve more attention both by clinicians and pathologists. Unfortunately it remains undervalued and underutilized even if it could be a powerful tool in the clinical, scientific and medicolegal field.

Development and use of precise definitions of fetal or neonatal brain injuries must be a priority for clinical researchers. It is no longer acceptable to label every neonatal encephalopathy as hypoxic-ischemic or "birth asphyxia". To improve our understanding of the etiology of neonatal encephalopathy and the role that events and care during pregnancy and delivery have in its genesis, it will be mandatory the availability of a universally agreed definition of neonatal encephalopathy which does not presume etiology. The lack of a commonly agreed and accepted definition greatly inhibits our ability to both measure and monitor the incidence of such syndromes, and to investigate its causes and thus prevent, when it is possible, its occurrence.

As specific tools to define the causes and the time of fetal injury are lacking, at present obstetricians and neonatologists should be aware of the limitations rather than the power of the means now available.

Moreover, it should be avoided any inappropriate use of current criteria indicative of intrapartum events as they cannot be considered specific for birth asphyxia: their lack excludes an intrapartum hypoxic event, their presence is not enough to state that such an event has really occurred. Misuses are possible, especially in medicolegal preceedings.

Intrapartum emergencies can certainly contribute to fetal neurological injury thus they need an appropriate response. Moreover, since most injuries occur before birth, even with the best care not all damaging intrapartum events are avoidable.

Can we now prevent cerebral palsy? The answer of KB Nelson is: "there is little evidence at present that we can." (8)

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