Opinion Paper

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Perinatal brain damage – what the obstetrician needs to know

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Abstract: Perinatal brain damage is still one of the leading contributors to perinatal death and postnatal disability worldwide. However, the term perinatal brain damage encompasses very different aetiological entities that result in an insult to the developing brain and does not differentiate between the onset, cause and severity of this insult. Hypoxic-ischemic encephalopathy (HIE), intraventricular haemorrhage, periventricular leukomalacia and perinatal stroke are often listed as the major aetiologies of perinatal brain damage. They differ by type and timing of injury, neuropathological and imaging findings and their clinical picture. Along the timeline of neurodevelopment *in utero*, there appears to be a specific "window of vulnerability" for each type of injury, but clinical overlap does exist. In the past, peripartum acute hypoxia was believed to be the major, if not the only, cause of perinatal brain damage, but intrauterine inflammation, prematurity, chronic hypoxia/growth retardation and genetic abnormalities appear to be at least equally important contributors.

Keywords: cerebral palsy; hypoxic-ischemic encephalopathy; intraventricular haemorrhage; perinatal brain damage; therapeutic hypothermia.

Introduction

Perinatal brain damage is an umbrella term describing the result of an injury to the developing brain. The major causes are often listened as hypoxic-ischemic encephalopathy (HIE), intraventricular haemorrhage, periventricular leukomalacia and perinatal stroke, but only HIE will be covered in detail in this article.

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Sometimes cerebral palsy (CP) and encephalopathy of prematurity (EoP) are also listed as causes of perinatal brain damage, although they rather describe clinical syndromes or findings that may (or may not) be the result of perinatal brain damage.

Neonatal encephalopathy

Neonatal encephalopathy is a broad term to describe disturbed central nervous dysfunction in a near term (>35 weeks) neonate and may occur because of a wide variety of conditions. It is characterized by an abnormal level of consciousness with

- seizures
- depression of tone and reflexes
- difficulty in maintaining normal respiration
- difficulty in suckling/swallowing

Neonatal encephalopathy is associated with early mortality in the newborn and with long-term morbidity, including poor neurodevelopmental outcome. It is often challenging to determine the cause of neonatal encephalopathy since there is no gold standard for diagnosis.

Approximately half of term infants with moderate to severe neonatal encephalopathy have early evidence of brain injury on MRI. Predominant sites of injury on MRI are the basal ganglia (33.8%), white matter (WM) (33.5%) and cortex (25.6%) [1].

Hypoxic-ischemic encephalopathy

Hypoxic-Ischemic encephalopathy (HIE) is a non-specific term for brain dysfunction caused by a lack of blood flow and oxygen to the brain. The incidence of HIE differs considerably globally. HIE affects 1 (–3) per 1,000 live births in developed countries [2–4], but is considerably more frequent in the developing world [5]. In general, a third of severely affected neonates die and approximately 30–40% of survivors develop disabilities including seizures, motor, cognitive and memory impairment and cerebral palsy. Mild neonatal encephalopathy in term infants has a good prognosis and a high probability of normal follow-up. Early

normal neurologic examinations and normal brain MRI increases the chances of normal long-term development in patients after therapeutic cooling [6].

Pathomechanism

Hypoxia–ischemia of sufficient severity leads to a depletion of cerebral energy reserves, activates several pathways leading to cell death, including oxidative and mitochondrial stress, apoptosis, and microglial activation. Oxidative stress is particularly harmful to the neonatal brain due to the high consumption of oxygen and low concentrations of antioxidants when transitioning from foetal to neonatal life.

Even though there is some restoration of cerebral energy stores after cerebral reperfusion during the so-called latent phase, energy failure can recur during the following hours (secondary energy failure) to days (tertiary energy failure). The latent phase is considered the therapeutic window in neonatal HIE because cell death pathways that lead to secondary and eventually tertiary energy failure are ongoing. At least in theory, the progression of brain damage can be halted by preventing the onset of the secondary energy failure.

However, in many HIE cases multiple factors contribute to the neonatal brain damage. The exposure of the neonatal, immature brain to inflammatory stimuli can cause an increase in pro-inflammatory cytokine levels and neuronal cell death [7] and may increase the vulnerability of the developing brain to hypoxia. High concentrations of multiple inflammation-related proteins during the first two postnatal weeks were found to be associated with an increased risk of ventriculomegaly, while high concentrations of IL-6, IL-8, ICAM-1 were associated with an increased risk of an echolucent/hypoechoic lesion [8].

Bacterial infection increases the risk of intraventricular haemorrhage and brain damage and can directly induce brain inflammation in animal models [9].

Encephalopathy of prematurity (EoP)

The mechanism and clinical picture of prenatal brain damage in preterm infants differ from term infants. The most prominent findings of EoP in very preterm infants are

(1) decreased global brain volume due to white and gray matter (GM) reduction (both cortical GM as well as deep nuclear GM)
(2) hydrocephalus ex vacuo
(3) connectivity impairment

It is now proposed that inflammation could be a leading cause of preterm brain damage.

Inflammation, chronic hypoxia, hypoglycemia and oxidative stress are also believed to be the main contributors of the prenatal onset of brain damage in growth restricted foetuses [10], which is broadly characterized by reduced total brain volume, altered cortical volume and structure, decreased total number of cells and myelination deficits.

Cerebral palsy

Cerebral palsy (CP) is a clinical syndrome caused by non-progressive brain injury in the foetus or infant leading to lifelong disability. Cerebral palsy affects body movement, muscle control, muscle coordination, muscle tone, reflex, posture and balance. It can also impact fine motor skills, gross motor skills and oral motor functioning.

The aetiology of CP is complex, multifactorial and difficult to confirm in an individual child. Cerebral palsy occurs mainly in preterm infants, but HIE in term infants has also been associated with CP to a variable degree. The incidence of cerebral palsy in neonates with and without an acute hypoxic event around birth differs in relation to the studied populations ranging from <10% to >30% [11, 12]. Being small for gestational age (SGA) at term might be an important risk factor cerebral palsy [12, 13] irrespective of an intrapartum hypoxic event. Diagnosing hypoxic-ischemic encephalopathy and cerebral palsy correctly is the major problem in clinical practice as well as in research, limiting our understanding of the contributing impact of perinatal hypoxia [14]. With the rapid development of genetic testing e.g. whole-exome-sequencing, an underlying genetic cause is found increasingly often (15–60%) depending on the type of CP [15–17].

Perinatal asphyxia

Perinatal asphyxia (or birth asphyxia) describes a condition of impaired gas exchange or inadequate blood flow leading to hypoxemia and hypercapnia that occurs in temporal relation to labour and delivery. HIE can be one of the resulting manifestations, but multi-organ dysfunction is common and can affect every organ, especially the respiratory and cardiovascular tract. Birth asphyxia is however an unspecific term and although the ACOG Committee on Obstetric practice recommended in 2005 not to use the term “birth asphyxia” anymore, it is still found in current literature.

Obstetric events and perinatal brain damage

Obstetric emergencies such as placental abruption, uterine rupture, umbilical cord prolapse or shoulder dystocia, but also maternal cardiac arrest or pulmonary embolism can lead to acute foetal hypoxemia and severe neonatal brain injury. These events are often unpredictable and therefore largely unpreventable. Depending on the definition, acute sentinel events are responsible for 15–35% of HIE [2]. The majority of foetal hypoxia is accordingly not related to an acute "sentinel event" but rather to a mismatch of foetal demand and placental capacity during labour.

Uterine contractions lead to increased intrauterine pressure (25–70 mmHg) and a decrease in placental blood flow (up to 60%) and placental oxygenation. This leads to a decline in foetal partial arterial oxygen pressure (PaO_2) by approximately 25% and transient foetal and placental hypoxia. A healthy term foetus with a normally developed placenta can accommodate this transient hypoxia by activation of [18]:

- the peripheral chemoreflex to increase sympathetic and parasympathetic activity
- resulting in a reduction in oxygen consumption and a centralization of oxygenated blood to critical organs (heart, brain, and adrenals)

Placental dysfunction due to impaired placentation or uterine hyperstimulation predisposes the foetus to intrapartum foetal compromise. Foetal decompensation occurs if the foetus cannot maintain its cardiac output. Progressive hypoxia in labour results in a further reduction of myocardial glycogen stores and impaired cardiac function, leading to profound systemic hypotension and irreversible multiorgan injury.

Many studies are accumulating evidence that there are often antenatal risk factors present in neonates that develop neonatal encephalopathy due to hypoxic-ischemic events around the time of delivery [19]. Often neither the underlying condition (risk factor) nor one single event during labour can sufficiently explain the clinical picture of encephalopathy in the affected neonate. Similarly, in a retrospective multicentre cohort of newborns with HIE, a combination of acute and chronic placental abnormalities (43%) was more common than either acute (20%) or chronic (21%) abnormalities alone [20]. Probably there is either an "acute on chronic" event during labour and delivery or a continuous deterioration during pregnancy in most of the cases.

Unfortunately, our ability to detect the foetus "at risk" before or during labour is still frustratingly bad. In a recent study in the UK for example, only 25% of cases with moderate to severe HIC were in retrospect detected by abnormal CTG findings with a 95% specificity >1 h before delivery [21]. Foetal growth monitoring and Doppler ultrasound can detect the severely compromised preterm foetus, but not reliably the foetus at term that will decompensate during labour and delivery.

Risk factors for HIE

Risk factors for neonatal encephalopathy, that have been identified in population based studies, can be assigned to three major groups: infection/inflammation, e.g. chorioamnionitis, chronic malperfusion/hypoxia, e.g. in fetal growth restriction and preterm delivery/prematurity. Factors that are often not considered are maternal socioeconomic status and health history, family history of neurologic disease and the impact of genetics/epigenetics [22].

Maternal obesity seems to be another independent risk factor. In a retrospective study of 97,488 pregnancies, infants of obese mothers were diagnosed with HIE more frequently than infants of non-obese mothers (OR 1.96), even after adjusting for type of delivery and maternal risk factors [23].

Therapy of HIE

Therapeutic hypothermia is currently the only available treatment that has been proven to improve neurologic long-term outcome in term and late preterm infants with HIE. Cooling reduces brain metabolism, thus subsequently decreasing the secondary energy failure phase that follows the acute hypoxic-ischemic insult. Cooling should be started within 6 h to be neuroprotective, data regarding later initiation of treatment is limited.

Therapeutic hypothermia improves survival and neurodevelopmental outcome at 18 months (48 vs. 63%, risk ratio 0.75) [24, 25] and decreases CP (risk ratio 0.66) [26].

Other potential therapeutic candidates focus on reducing oxidative stress and inflammation following the primary injury but have either not yet reached the stage of clinical trials or have not been proven to be effective.

Conclusions

Perinatal brain damage is often multifactorial and our understanding of the individual causes and contributing factors is still surprisingly limited. Acute hypoxic events during

delivery may play a less important role than previously believed, especially in high resource settings, where intrauterine inflammation, prematurity, chronic hypoxia/growth retardation and genetic abnormalities appear to be more important contributors.

Correctly identifying the unborn foetus 'at risk' for adverse neurologic outcome at any gestational age remains a major problem in obstetric practice. Currently we still attempt to predict adverse outcome during labour by monitoring foetal growth and heart rate patterns before and during labour, measuring Doppler flow, amniotic fluid or foetal movements – and we still cannot predict with confidence if a foetus is already hypoxic, in danger of becoming hypoxic or is chronically hypoxic but well adapted to the situation. For foetal monitoring to help improve clinical outcomes, it must be able to predict adverse outcomes with acceptable accuracy before hypoxia results in neuronal brain injury. However, hypoxemia may not be the only cause of neonatal HIE, which may develop secondary to renal, hepatic, and especially cardiac dysfunction. Therefore, a therapy that minimizes tissue injury in general, may have advantages over one that is specifically targeted to only the neurological sequelae of hypoxia.

As out knowledge grows about the different components and contributing factors of neonatal brain damage, we also need to reevaluate the experimental models that are used in research because they focus primarily on hypoxia as the sole cause of neonatal encephalopathy and cerebral palsy.

As obstetricians, while we are waiting and hoping for novel therapeutic options, as stem cell therapy, to be tested in larger clinical trials, we need to work on improving monitoring before and during labour and delivery to help select suitable candidates for these studies. In addition, together with researchers from various fields, we need to work on refining diagnosis and definition of the different types of perinatal brain damage and define outcome sets for future studies to be of clinical value for our patients, if we want to be able to evaluate the effect of any preventative or therapeutic measures on perinatal brain damage in the future.

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