Theme

Management of hypoxic-ischemic encephalopathy – current issues for the paediatrician

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Abstract

Perinatal asphyxia (PA) is defined as the deprivation of oxygen occurring around the time of birth. Hypoxic-ischemic encephalopathy (HIE) is an encephalopathy due to PA. Perinatal asphyxia and HIE are still associated with high morbidity and mortality rates. The use of therapeutic hypothermia (TH) commencing preferably within the first 6 hours of life – currently the only scientifically validated treatment modality for HIE – has been proven to reduce the mortality rate and disability. We discuss pathophysiology, diagnosis, neuroimaging, treatment, the impact of PA and TH on pharmacology, follow-up, and some remaining questions of PA and HIE. The purpose of this article is to guide the general pediatrician in selecting the patients for neuromonitoring and TH and inform them about the tools for outcome assessment and early intervention for those with high risk for impaired neurodevelopmental outcome.

Introduction

Perinatal asphyxia (PA) is defined as the deprivation of oxygen occurring around the time of birth. Hypoxic-ischemic encephalopathy (HIE) is an encephalopathy due to PA (1). In industrialized countries, its incidence is estimated to 1-5/1000 births (20-30/1000 in developing countries) (2). Mortality remains high (10-15%) and 25% of the survivors will develop a neurological impairment such as cerebral palsy, developmental delay, blindness, deafness, seizures and long-term neurological disability during childhood (1).

The therapeutic gold standard for moderate and severe forms of HIE is therapeutic hypothermia (TH) starting preferably within 6 hours of life for a duration of 72 hours. Randomized controlled studies have shown a significant reduction in death and disability at 18 months and improved neurodevelopmental outcome at 6-7 years (1). Therapeutic hypothermia is currently the only effective, and scientifically validated treatment for HIE, with a number needed to treat of 7 (1).

The purpose of this article is to summarize what is known about HIE and TH, useful for the general pediatrician taking care of newborns at delivery. We discuss pathophysiology, diagnosis, neuroimaging, treatment, the impact of PA and TH on pharmacology, and follow-up. In addition, the indications for transfer to a neonatal intensive care unit (NICU) in the context of PA, as well as unanswered questions about future perspectives, are discussed.

Pathophysiology of HIE

The pathophysiological mechanisms behind HIE are complex and can be divided in 3 phases (Figures 1 and 2) (3). The first phase of primary energy failure results from cerebral blood flow interruption (i.e. the primary neuronal insult) with reduced supply of oxygen and glucose and leads to an anaerobic metabolism as well as immediate neuronal death by necrosis. A transient recovery of cerebral oxidative metabolism after resuscitation maneuvers, i.e. the latent phase, precedes a secondary phase of delayed, progressive leading to mitochondrial collapse, cytotoxic oedema, increased production of free radicals, inflammatory mediators (neuroinflammation) and excitatory neurotransmitters. This leads to delayed neuronal apoptosis and extensive programmed cell death (3, 4). These events resolve over approximately 72 hours. A tertiary phase describes the ongoing effect on brain connectivity, maturation, and myelinization. These events could last between weeks to years after the perinatal insult and can explain the broad range of long-term neurological sequelae described in the affected patient population (3).

Diagnosis of HIE

Hypoxic-ischemic encephalopathy is a specific diagnosis that applies when a neonate suffers from an encephalopathy that is highly suspected to be due to a hypoxic-ischemic event. The causes of this event can be subdivided into maternal, placental, cord-related, foetal, traumatic and postnatal factors. A difference is made between an acute, severe event (sentinel event) such as umbilical cord prolapses, placental abruption or uterine rupture resulting into a possible near total asphyxia, or less severe events often leading to subacute, partial asphyxia (5).

An asphyxiating injury is often accompanied by systemic hypotension, leading to multi-organ failure. A newborn with neonatal encephalopathy (NE) can present with an abnormal state of consciousness, abnormal behaviour, respiratory difficulties, seizure activity, poor tone or posturing and absent reflexes. In cases where HIE is the cause of NE, the clinical signs of encephalopathy appear immediately after birth or within the first few hours of life.

Since a sentinel event is not always present peripartum, determining HIE as being the cause of a NE is not always straightforward and the differential diagnosis of NE should be kept in mind. Other aetiologies for NE such as multiple perinatal strokes, metabolic abnormalities, brain anomalies or infections are the more common differential diagnosis and must be quickly excluded.

Figure 1 : *Flow chart showing the mechanisms contributing to each phase of the evolution of neonatal encephalopathy over time. From Davidson et al. Update on mechanisms of the pathophysiology of neonatal encephalopathy (3). Reprinted with permission from Elsevier.*

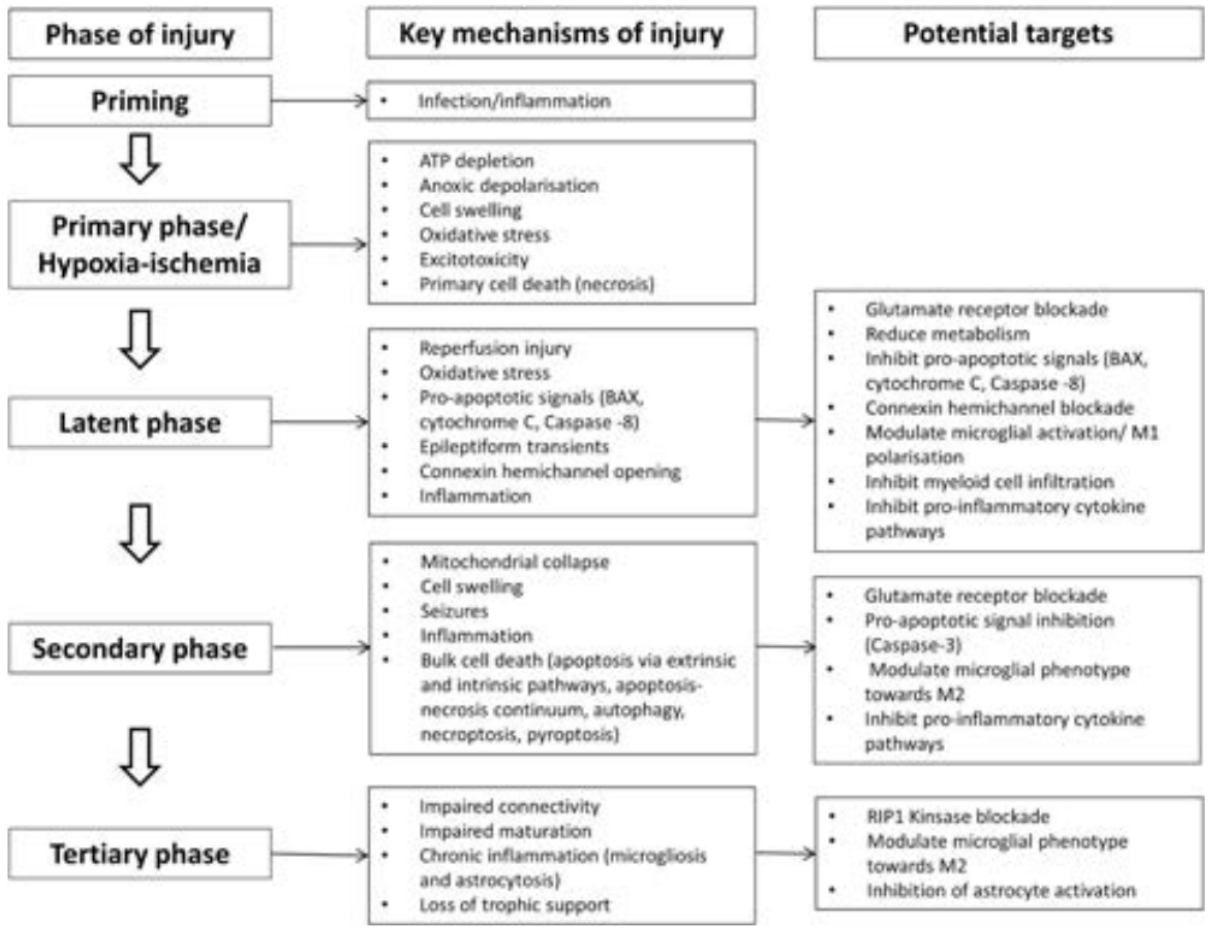


Figure 2 : *Pathophysiology of hypoxic-ischemic encephalopathy – First and second phase. Figure courtesy from Cornette et al. (30).*

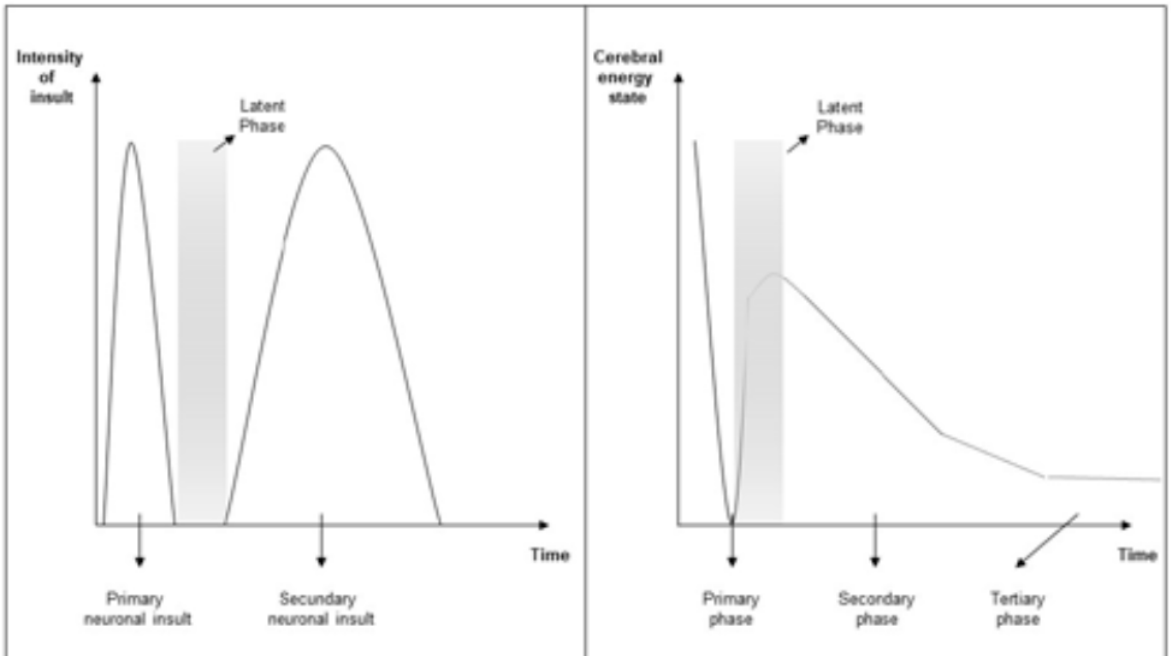
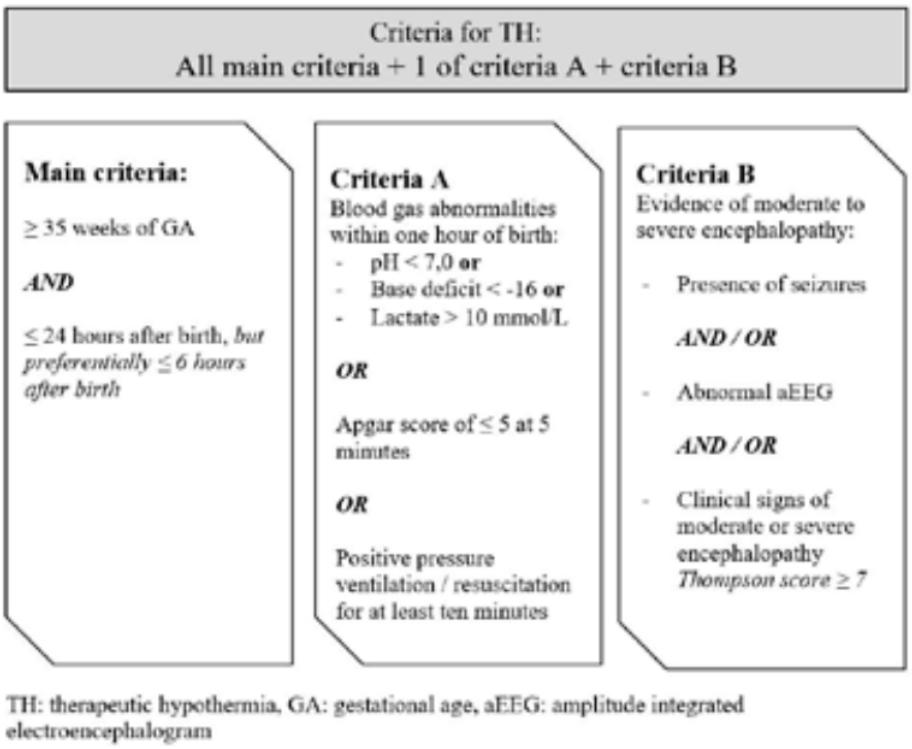


Figure 3 : *Criteria for therapeutic hypothermia.*



TH: therapeutic hypothermia, GA: gestational age, aEEG: amplitude integrated electroencephalogram

(although some centres are now including neonates as early as 34 weeks GA) *and > 1800 g* (6).

The *criteria for peripartum asphyxia* in TH studies, with each enrolled neonates with at least one of these criteria, consist of:

- Blood gas abnormalities on cord blood or within one hour of birth or after resuscitation for postnatal collapse: pH < 7.0 or base deficit < -16 or lactate □ 10 mmol/L
- Apgar score of ≤ 5 at 5 minutes
- Positive pressure ventilation / resuscitation for at least ten minutes

While the criteria for PA can be established bedside, and are based on objective evidence, establishing the degree of encephalopathy is more complicated. However, the *presence of an abnormal neurological examination* after PA supports the presence of HIE. Depending on the severity of the primary injury, and the presence of (evolving) brain damage, the clinical picture may evolve during the first hours after birth. Early recognition of moderate to severe encephalopathy is primordial to select eligible neonates for timely referral for TH. Careful clinical examination and especially the use of available clinical scoring systems, can distinguish between mild, moderate and severe encephalopathy. In addition, neuromonitoring devices like electroencephalogram (EEG) / amplitude integrated electroencephalogram (aEEG) are available to explore cerebral activity, in support of the HIE diagnosis. Both the clinical as well as the neuromonitoring tools are further described below.

Clinical diagnosis of HIE based on clinical scoring systems

The presence and severity of HIE can be estimated by 2 scoring systems: the modified Sarnat scale (Table 1) and the Thompson score (Table 2).

The Sarnat scale distinguishes 3 stages of HIE. The scale was first published in 1976 and it was intended to facilitate the formulation of neurologic diagnose the severity of HIE within the first hours after birth based on clinical examination alone (8).

However, the (modified) Sarnat score, although still widely used by general paediatricians, leaves much to individual interpretation of certain clinical criteria and is often misinterpreted. In a NICU environment, the Thompson score, a practical and more objective point system, is therefore preferred to determine the degree of encephalopathy and to decide whether the neonate should be subjected to TH. A good correlation with the Sarnat scoring system has been described. The Thompson score consists of clinical assessment of nine signs with a maximum score of 22. A Thompson score ≥ 7 between 1 and 3 hours of age suggests a moderate to severe clinical encephalopathy and is used as a criterion to start with TH (Figure 3, Table 2) (9). If there is doubt about possible HIE, or in case of a Thompson score of 5 after one hour which increases during the next hour a transfer to a NICU is recommended.

Neurological assessment of the newborn should be done as early as possible and should be repeated during the first hours of life to assess a detrimental progression of the encephalopathy.

Diagnosis of HIE based on neurophysiology

An early EEG on admission can provide insight in the cerebral activity of asphyxiated newborns. Term newborns who suffered from peripartum hypoxia often show EEG patterns in line with the severity of the hypoxic moment. Usually, the amplitude and the continuity of the background pattern are impaired for the first 6 to 8 hours of extra-uterine life, and then improve or worsen with the possibility of the emergence of seizures. Several classifications of EEG patterns in the asphyxiated newborn have been established on these features. The most commonly used are the French 4-grade classification and the Murray classification (10, 11). When using the French classification, hypothermia is indicated for scoring equal to or above grade 2.

Unfortunately, full EEG acquisition is not available in all NICUs 24 hours a

Table 1 : *Modified Sarnat scoring system. Predominant clinical features in stage 2 and/or stage 3 are an indication to start with therapeutic hypothermia. From Sarnat et al. Sarnat grading scale for neonatal encephalopathy after 45 years: an update proposal (8). With permission from Elsevier.*

Clinical Feature	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Spontaneous movement	Frequent symmetrical	Decreased	Absent
Autonomic system	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable (loss of heart rate variability)
Gastrointestinal motility	Normal or decreased	Increased; passing meconium	Variable
Primitive reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong	Weak; incomplete	Absent
Tonic neck	Slight	Strong	Absent
Olfactory response	Strong	Weak	Absent
Myotendon stretch reflex	Brisk	Brisk	Absent
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Normal or mild distal flexion	Strong distal flexion	Intermittent decerebration, fisting, thumb adduction
Central tone	Normal	Decreased	Flaccid

available, alternative technique. The aEEG trace is obtained by an algorithm calculated from a standard 2 or 4-electrode EEG acquisition. This cot side technique is now worldwide in use for the inclusion in the TH protocol and the brain monitoring of the asphyxiated newborn during the process. The visual analysis of an aEEG can be done bedside and is based on the lower and upper margins (voltages) of the recorded band (Table 3 and Figure 5). The level of the lower margin provides information on the EEG background. The bandwidth variation informs on the reactivity of the brain activity and the existence of a sleep-wake cycle. Marked and sudden changes of the lower margin and bandwidth suggest the occurrence of seizures (Figure 5). Several classifications for aEEG interpretation exist. Most often used is the classification of Al Naqeeb revised in 2006 by Hellstrom-Westas (12,13). According to these classifications, it is now accepted that the return of a sleep-wake cycle before 12 hours of life or a normalization of the background pattern within the first 6 hours of life are associated with a favorable neurological outcome. Therefore, aEEG represents an important tool to include patients in the TH protocol, to diagnose the occurrence of seizures, to monitor the effect of anti-epileptic drug treatment, and to assess evolution of cerebral activity over time (10).

Neuroimaging in HIE

Although cranial ultrasound can still play a role in the full-term infant with HIE, brain magnetic resonance imaging (MRI) is the method of choice to identify brain lesions and lead to a prognosis (14). Diffusion-weighted imaging (DWI) obtained between days 4 and 7 after the insult are most informative. DWI is based on the molecular diffusion of water and it best illustrates the cytotoxic oedema and, consequently, cell death. Brain swelling, even if initially severe, disappears by the second week after the insult and the DWI "normalizes". Therefore, brain MRI sequences (T1, T2 and DWI) are ideally performed after the cooling and the rewarming periods between days 4 and 7 (14).

Different patterns of brain injury have been described according to the severity and duration of the hypoxic-ischemic insult. They can be classified into two main patterns.

- The basal ganglia-thalamus (BGT) pattern affects the central grey nuclei and perirolandic cortex. This pattern is most seen after an acute and intense hypoxic event (e.g. cord prolapse, placenta abruption, etc.). At birth, newborns are severely depressed and need resuscitation. Neonates with the BGT pattern tend to be severely handicapped and suffer from motor disorders and learning difficulties. Depending on the severity of the BGT injury and the involvement of the posterior limb of the internal capsule (PLIC), the neurological prognosis varies (14).
- The watershed predominant (WS) pattern of injury is seen

Table 2 : *Thompson scoring system. A Thompson score of ≥7 is an indication for therapeutic hypothermia.*

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
Consciousness	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	Normal	Infrequent < 3/day	Frequent > 2/day	
Posture	Normal	Fisting / cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent / bites	
Respiration	Normal	Hyperventilation	Brief apnoea	Apnoea / IPPV
Fontanel	Normal	Full	Tense	

Figure 4 : *Clinical setting of therapeutic hypothermia. Figure courtesy from Cornette et al. (26).*

cerebral arteries. In the more severe case, the overlying cortex is also involved. The lesions can be unilateral or bilateral, anterior and/or posterior. Neurological manifestations at birth may be mild and do not always meet the criteria for cooling. Children with the WS pattern are more at risk of cognitive deficits, language delay and/or behavioral problems (14).

Treatment of HIE

Therapeutic hypothermia involves actively reducing the body temperature to 33.5 degrees Celsius during 72 hours, which acts as a neuroprotector (see Figure 4 for the setting). Neither deeper cooling (32°C) nor a longer duration of TH showed any benefit (15). The hypothermic period is followed by controlled rewarming (increase of temperature with 0.5°C per hour) up to 36.5°C. Subsequently, a temperature of 36.5°C is maintained for 24 hours. According to the currently available Flemish-Dutch guidelines, start of the hypothermia treatment is possible within the first 24 hours after birth, but preferably before 6 hours of age (6).

Hypothermia may modify cells programmed for apoptosis, leading to their survival. It may also protect neurons by reducing cerebral metabolic rate, attenuating the release of excitatory amino acids and lowering production of toxic nitric oxide and free radicals. TH aims to limit this delayed apoptosis by decreasing cerebral energy metabolism (5 to 8% per degree) and cerebral blood flow (and consequently cerebral edema). A specific action on the excitotoxic cascade and the activation of neuroprotective genes have also been demonstrated (4).

There is increasing preclinical evidence that late, neurorestorative interventions have potential to improve the overall outcome. In the so-called "hypothermia plus" studies, TH is combined with the administration of an extra molecule that shows to be neuroprotective in animal studies. For example, the free radical antagonist melatonin as well as the anti-excitotoxic gas Xenon, might be able to extend the therapeutic window for hypothermia, potentially by suppressing free radical release and excessive glutaminergic activity during the early phase of recovery from hypoxia-ischemia (3, 16). An ongoing study in which several Belgian units participate combines TH with the administration of allopurinol (or placebo) in the first 30 minutes of life (ALBINO trial, www.albino-study.eu). Allopurinol is a xanthine oxidase inhibitor and, if administered early after the insult, it reduces the production of oxygen radicals and brain damage in experimental, animal and preliminary human studies of cerebral ischemia. Furthermore, trophic factors such as EPO or IGF-1 can cross the blood-brain barrier and could boost neurogenesis (3, 16). Finally, studies in which mesenchymal stem cells are administered by intranasal route are promising, as such may enhance brain plasticity (3).

Impact of asphyxia and hypothermia on pharmacology

Neonates with PA treated with TH often need multiple drug therapy. Asphyxia and hypothermia both influence physiology, and consequently also pharmacokinetics (PK) and pharmacodynamics. Their impact on the 4 main PK steps (absorption, distribution, metabolism and excretion) is described in a recent review (17). Absorption data are limited since the intravenous route

Table 3 : *Amplitude-integrated electroencephalogram classification*

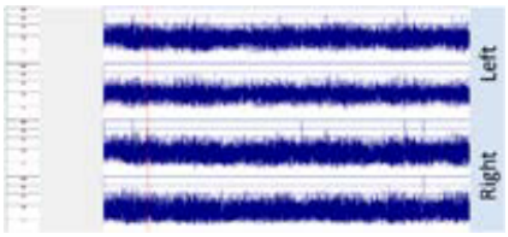
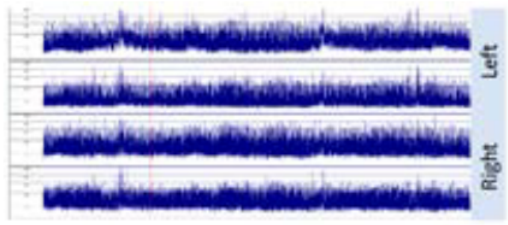
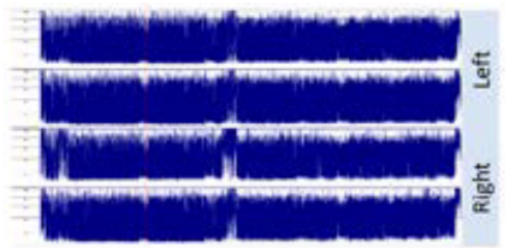
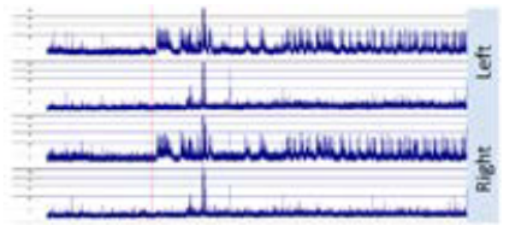
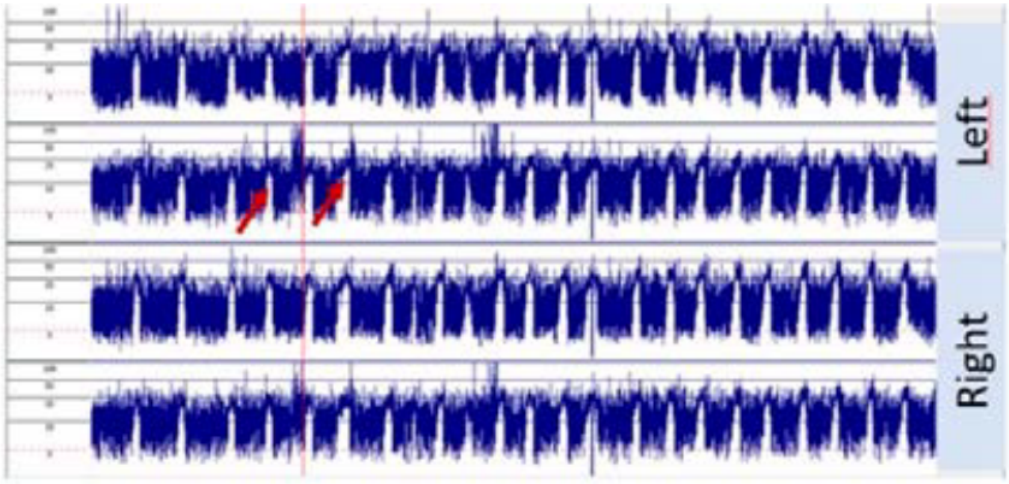
al Naqeeb classification (1999) (12)	Hellström – Westas classification (2006) (13)	aEEG typical tracing
Normal: lower limit > 5 µV and upper limit > 10 µV	**Normal:** continuous trace of normal voltage, sleep wake cycling lower margin > 5 µV and upper margin > 10 µV	
Moderately abnormal: lower margin ≤ 5 µV and upper margin > 10 µV	**Discontinuous:** lower margin < 5 µV and upper margin > 10 µV	
	Burst suppression: lower margin < 5 (0-1) µV and upper margin > 25 µV	
Severely abnormal: lower margin < 5 µV and upper margin < 10 µV	**Low voltage:** lower margin < 5 µV and upper margin < 10 µV	

Figure 5 : *Amplitude-integrated electroencephalogram (aEEG) in an asphyxiated newborn, day 1. The trace is discontinuous with the lower margin of the aEEG band < 5µV. Each rise in the lower margin indicates a seizure episode (2 examples indicated by red arrows).*



is usually applied during TH (18). Volume of distribution can increase (+30% for ampicillin), decrease (-37% for morphine) or remain unchanged during hypothermia. While knowledge on the impact of PA and TH on renal drug excretion increases, the mechanisms explaining impact on drug metabolism need further research (18). Overall, clearance of drugs undergoing metabolism (e.g. morphine) is often decreased in this population. Decreased clearance is most pronounced for renal drug elimination, like aminoglycosides (gentamicin -25 to -35%, amikacin -40%) (17, 19) or beta-lactam antibiotics (17). The renal impact is also obvious in physiology data. Serum creatinine values at birth up to 48h are higher in neonates with PA and TH compared to reference 50th centile values. After 48h a declining trend towards high(-normal) creatinine is observed (20). Based on above mentioned examples it is clear that adapted dosing for some compounds during TH is recommended, to avoid drug accumulation and toxicity. Therapeutic drug monitoring for selected drugs, and observation of clinical effects in this setting, are needed to further individualize dosing.

Follow-up

The current rate of death or disability following TH at 33.5°C for 72 h for moderate/severe HIE is 29% of whom 23% of survivors were identified with cerebral palsy (1). Assessment of the severity of brain damage and prediction of outcome is essential to determine intensive care management and to ensure adequate parental counselling.

In general, outcome corresponds to the severity of clinical grading of encephalopathy, and moderate to severe grades will have the highest rates of disability and mortality (1, 5). Many predictors have been studied to evaluate the prognosis for the individual patient, including clinical history, EEG/aEEG, near-infrared spectroscopy and MRI (11,13,21-23). It is necessary to remember that HIE is a dynamic process and the greatest prognostic accuracy for predicting long-term neurological outcome is likely to be obtained by combining repeated clinical examination with neurophysiological tests, as well as brain MRI in the first week of life, whether or not the neonate is treated with TH.

It is important to inform parents of their neonate's situation as soon as possible, and meetings with the parents should be repeated regularly. This permits them to fully understand the current situation of their child and offers them a sense of control and safety (24). Parents are initially often in a state of shock, and they need clear information particularly regarding the diagnosis of HIE and the treatment decisions that might be made within hours of arrival in the NICU (25). As the end of the hospital stay approaches, it is also very

Remaining questions

The key issue remains whether we should use TH for mild encephalopathy and inclusion beyond 6 hours of life.

Therapeutic hypothermia initiated before 3 hours of life has been shown to be more effective than TH initiated between 3 and 6 hours of life. Although TH initiated between 6 and 24 hours of life may have benefit, its effectiveness is still uncertain (6, 26). If, unfortunately, it has not been possible to start TH before 6 hours of life, we should still consider it up to 24 hours, depending on the evolution of the clinic and the complementary information (biological and neurophysiological) (6)

Furthermore, 50% of HIE develop mild encephalopathy that does not meet the criteria for TH. Their outcome was previously considered as normal but several studies have shown that approximately 20-25% of these patients have an unfavorable short-term and long-term outcome (with significant reduction in IQ and language skills, neuropsychological difficulties, autism, epilepsy, visual and sensory loss and higher rates of learning impairment) (27). Brain imaging of these neonates with mild encephalopathy may show detectable abnormalities on MRI, even after TH (28). However, meta-analyses have failed to determine the benefit of hypothermia in this category of patients (29).

In any case, whenever there is some doubt about the severity of HIE, discussing the case with a NICU immediately after birth is essential. This may lead to a timely referral to a NICU with EEG-expertise to help grading the HIE and to decide whether to cool or not.

Conclusion

Hypoxic-ischemic encephalopathy remains a major cause of neonatal mortality and long-term neurodevelopmental sequelae in industrialized countries. Therapeutic hypothermia has been proven to reduce the mortality rate and disability of the term and near-term neonates presenting with moderate or severe HIE in the context of perinatal asphyxia. Timely discussion and transfer to a NICU is therefore imperative for any neonate with perinatal asphyxia in whom there is doubt about the indication for therapeutic hypothermia.

Conflicts of interest statement

The authors of this review declare that they have no conflict of interest. They do not have any affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this review.

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