

Short and long term prognosis in perinatal asphyxia: An update

Caroline E Ahearne, Geraldine B Boylan, Deirdre M Murray

Caroline E Ahearne, Geraldine B Boylan, Deirdre M Murray,
Department of Paediatrics and Child Health, University College Cork,
Cork T12 YN60, Ireland

Caroline E Ahearne, Geraldine B Boylan, Deirdre M Murray,
Irish Centre for Fetal and Neonatal Translational Research (INFANT
Centre), University College Cork, Cork T12 YN60, Ireland

Author contributions: Ahearne CE aided in the literature review, and contributed to the text and preparation of the manuscript; Boylan GB contributed to the manuscript and edited final content; Murray DM wrote and edited the manuscript.

Supported by The Health Research Board CSA/2012/40; and a Science Foundation Ireland Research Centre Award (INFANT - 12/RC/2272).

Conflict-of-interest statement: There is no conflict of interest associated with either of the authors who contributed to this manuscript.

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Correspondence to: Dr. Deirdre Murray, Department of Paediatrics and Child Health, University College Cork, Western Rd, Cork T12 YN60, Ireland. d.murray@ucc.ie
Telephone: +353-21-4205023

Received: July 31, 2015

Peer-review started: August 3, 2015

First decision: October 13, 2015

Revised: November 18, 2015

Accepted: December 17, 2015

Article in press: December 18, 2015

Published online: February 8, 2016

Abstract

Interruption of blood flow and gas exchange to the fetus in the perinatal period, known as perinatal asphyxia, can, if significant, trigger a cascade of neuronal injury, leading on to neonatal encephalopathy (NE) and resultant long-term damage. While the majority of infants who are exposed to perinatal hypoxia-ischaemia will recover quickly and go on to have a completely normal survival, a proportion will suffer from an evolving clinical encephalopathy termed hypoxic-ischaemic encephalopathy (HIE) or NE if the diagnosis is unclear. Resultant complications of HIE/NE are wide-ranging and may affect the motor, sensory, cognitive and behavioural outcome of the child. The advent of therapeutic hypothermia as a neuroprotective treatment for those with moderate and severe encephalopathy has improved prognosis. Outcome prediction in these infants has changed, but is more important than ever, as hypothermia is a time sensitive intervention, with a very narrow therapeutic window. To identify those who will benefit from current and emerging neuroprotective therapies we must be able to establish the severity of their injury soon after birth. Currently available indicators such as blood biochemistry, clinical examination and electrophysiology are limited. Emerging biological and physiological markers have the potential to improve our ability to select those infants who will benefit most from intervention. Biomarkers identified from work in proteomics, metabolomics and transcriptomics as well as physiological markers such as heart rate variability, EEG analysis and radiological imaging when combined with neuroprotective measures have the potential to improve outcome in HIE/NE. The aim of this review is to give an overview of the literature in regards to short and long-term outcome following perinatal asphyxia, and to discuss the prediction of this outcome in the early hours after birth when intervention is most crucial; looking at both currently available tools and introducing novel markers.

Key words: Perinatal asphyxia; Neurological outcome; Hypoxic ischaemic encephalopathy; Cerebral palsy; Cognitive

outcome

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Core tip: Perinatal asphyxia is a significant cause of acquired brain injury occurring in the neonatal period. A reliable early marker for predicting injury severity and sequelae remains elusive. The advent of therapeutic hypothermia as an effective neuroprotective intervention has changed the prognosis for affected infants. In this review we summarise what is known about the short and long term outcome for infants with perinatal asphyxia in the pre- and post-cooling era. We also describe currently available early indicators of outcome and introduce the exciting field of emerging novel biomarkers, both chemical and physiological.

Ahearne CE, Boylan GB, Murray DM. Short and long term prognosis in perinatal asphyxia: An update. *World J Clin Pediatr* 2016; 5(1): 67-74 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v5/i1/67.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v5.i1.67>

BACKGROUND

Perinatal asphyxia describes the interruption of blood flow or gas exchange to and from the fetus in the perinatal period^[1]. This may be prolonged partial asphyxia, sudden sub-total asphyxia due to a sentinel event or a combination of both^[2]. Hypoxic-ischaemic injury to the brain and vital organs may result if the perinatal asphyxia is of a sufficient degree or prolonged beyond the ability of the fetus to compensate^[3-5]. Approximately 20 per 1000 deliveries will require significant resuscitation, with biochemical and clinical evidence of perinatal asphyxia^[6]. Of these only 1.6 per 1000 will go on to develop signs of evolving encephalopathy consistent with hypoxic-ischaemic encephalopathy (HIE)^[7]. HIE must be differentiated from other causes of neonatal encephalopathy (NE), such as sepsis, meningitis or a metabolic disorder^[1,8,9]. There may be a high suspicion of hypoxic-ischaemic injury following a known perinatal insult such as placental abruption or cord accident or if typical clinical signs, biochemical evidence of metabolic acidosis or depressed Apgar scores are present. However it can be very difficult to make this differentiation quickly after birth^[10]. Approximately 50%-80% of NE can be attributed to hypoxia-ischaemia and given the potential benefit of early treatment, the need to identify infants with hypoxic-ischaemic induced encephalopathy is becoming increasingly important^[1,11-13].

The aim of this review is to provide an overview of the literature on short and long-term outcome following perinatal asphyxia in the pre- and post-cooling era. We also aim to discuss the ability of currently available tools and novel markers to predict outcome in the early hours after birth when intervention is most crucial.

CURRENT MARKERS FOR PREDICTION OF OUTCOME

The advent of therapeutic hypothermia as a neuro-protective treatment for those with moderate and severe encephalopathy has improved prognosis^[14,15]. Hypothermia is, however, a time sensitive intervention, with a very narrow therapeutic window and must be instigated within 6 h or ideally sooner following delivery to be effective^[16]. So the challenge has become the prompt identification of those infants with signs of perinatal asphyxia who are most at risk of developing moderate or severe HIE. Prompt identification of those who will benefit from current and emerging neuroprotective therapies will help guide appropriate application of resources and permit prognostication. Currently available indicators such as blood biochemistry, clinical examination and electrophysiology all have limitations and their predictive power has been affected by the interceding intervention of therapeutic hypothermia; yet they still remain at the core of our predictive armamentarium in the critical first postnatal hours (Table 1).

Acid-base balance

A disturbance in acid-base balance is one of the earliest and most sensitive signs of fetal distress. The degree of acidosis is measured by scalp or cord pH, with acidosis being used to determine the need for intervention. A pH of < 7.00 gives a 50% chance of abnormal outcome, however the positive predictive value for significant encephalopathy is low^[17]. This prediction might be improved by focusing on metabolic acidosis, and in particular lactate level. However several large trials have shown that lactate monitoring during labour does not improve our ability to detect or prevent adverse labour outcomes compared to pH monitoring alone and may in fact increase rates of instrumental deliveries unnecessarily^[18,19].

Apgar score

Almost all infants are scored at birth through the eyes of Virginia Apgar, with midwives worldwide using her score for describing the condition of the infant at birth. However, Apgar scores suffer from poor sensitivity and specificity, as 80% of those with an Apgar score of ≤ 7 at 5 min will have a normal outcome^[17]. Often felt to be useful at extremes, 1 in 5 babies with an Apgar score of 0 at 10 min will survive to school age without moderate or severe disability^[20]. A further difficulty is the subjective nature of the Apgar score, which leads to high levels of inter-observer variability. Subjective real time clinical scores have been shown to overestimate Apgar scores by a median value of 2.4 compared to later video enhanced estimation^[21]. Attempts have been made to improve on the conventional Apgar score with Expanded and Combined versions that take aspects of neonatal resuscitation into account^[22,23]. In particular, the Combined Apgar score at 5 min after birth has shown some promise in the prediction of perinatal acidosis

Table 1 Predictors of outcome

Predictors of outcome	Pros	Cons
Standard		
Acid-base balance	Widely available test, can be measured early by scalp and cord sampling	Cannot differentiate degree of severity of injury, invasive testing
pH	Responds early to HI	Low PPV for abnormal outcome
Lactate	Better reflects metabolic mechanism	No advantage over pH
Apgar score	Quick assessment of neonatal condition at birth, non-invasive	High inter-observer variability, poor predictor of long-term outcome
Clinical examination	Non-invasive, good to track changes in clinical state as injury evolves, predictive at discharge	Requires clinical experience, affected by intubation and medications and hypothermia, poor predictor of long-term outcome
EEG/aEEG	"Gold standard", early predictive value if normal, value of subclinical seizure detection, non-invasive	Requires resources, equipment to apply, clinical expertise to interpret
Novel		
HRV	Differentiates severity of HIE, non-invasive	Requires specialist equipment
MRI/MRS	Specific patterns of injury aid prognosis, early changes apparent	Requires specialist equipment, requires transfer of sick infant to MRI machine/department, requires infant to remain still for prolonged periods
Biomarkers	Very promising in pilot studies	None validated for clinical use
Serum	Reflects systemic biochemical state	Mixed markers from cerebral and other organ dysfunction, only small volumes available, invasive testing
Cord blood	Large volumes possible, available early	Mixture of fetal and placental blood
CSF	Reflects cerebral markers	Very difficult to sample
Urine	Relatively easy to sample	Affected if significant renal disease
Proteomics	Relatively stable and easy to test	Requires specialist equipment, response to injury may be delayed
Metabolomics	Rapidly responsive to changes in biochemical state	Requires specialist equipment, highly sensitive to environmental factors
Transcriptomics	Involved in critical processes of cell cycle and cell death, very stable	Requires specialist equipment, most markers are completely novel and difficult to identify, they may also regulate multiple pathways

The current standard tools and the novel emerging techniques to predict outcome in perinatal asphyxia are outlined with their respective advantages and disadvantages. HI: Hypoxia-ischaemia; EEG: Electroencephalograph; aEEG: Amplitude-integrated electroencephalograph; HRV: Heart rate variability; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; HIE: Hypoxic-ischaemic encephalopathy; CSF: Cerebrospinal fluid.

(sensitivity 97% and specificity 99%) and HIE ($P = 0.01$ if score is < 10), though it cannot distinguish severity of HIE, and long term outcome data is unavailable^[24].

Clinical examination

The neurological examination of a neonate is a clinical skill learnt through experience and exposure. Standardised scores have been developed, and widely used in an attempt to improve interobserver reliability^[25-27]. However, the examination of a sick neonate is hampered by the need for sedative medications, anti-convulsants and intubation. We have shown that in full term infants, the best prediction of outcome is achieved by the examination at discharge. Examination on the first day after birth, even using a standardised method is not good for the prediction of outcome at two years^[28]. More recent studies have shown that therapeutic hypothermia reduces our ability to accurately estimate the neurological state of the infant^[29].

Electrophysiological monitoring

Electroencephalography (EEG) and amplitude integrated EEG (aEEG) have both been shown to offer excellent predictive ability as early as 3-6 h following delivery^[30]. Outcome is strongly linked with the severity of EEG abnormalities seen. EEG and aEEG abnormalities evolve

over the first 72 h, and so the timing of the recording is crucial to interpretation^[31]. Early return of sleep wake cycling and normalization of background EEG abnormalities are good prognostic indicators^[32,33]. The link between prognostic ability and timing of this evolution is altered by therapeutic hypothermia, so that delayed recovery may still be associated with a normal outcome^[34]. A normal EEG recorded soon after birth is highly associated with a normal outcome at 2 years^[35]. However, an abnormal EEG soon after birth may recover over subsequent days but if it remains abnormal at 48 h a poor prognosis is highly likely^[35]. The PPV of a severely abnormal aEEG for death or disability at 6 h is 0.63 when assessed by the voltage grading scheme^[34] and 0.59 when the aEEG is assessed by the pattern grading scheme^[30,36,37]. These values drop slightly but not significantly in cooled infants^[34]. In experienced hands EEG or aEEG provide an accurate assessment of the grade of encephalopathy and are excellent adjuncts to clinical decision making.

Multichannel EEG monitoring is essential for the detection of neonatal seizures, which occur frequently in infants with moderate and severe HIE. These seizures are difficult to predict or detect clinically and are associated with poor prognosis^[38-41]. aEEG alone will miss focal or low amplitude seizures and requires expert interpretation^[42,43]. We hope that in the future cot-side automated seizure

detection tools will be available to improve detection, and thereby the treatment of seizures in HIE^[44].

NOVEL MARKERS FOR THE PREDICTION OF OUTCOME

There is increasing interest in the possibility of developing more accurate, early and reliable markers for predicting long term outcome in HIE. These bio- and physiomarkers may take the form of physiological monitoring [EEG and heart rate variability (HRV)], neuroradiological, or biochemical. In fact the ideal marker may be a combination of many of these (Table 1).

Reduced HRV has shown potential for the assessment of HIE severity and the prediction of long term outcomes^[45,46].

Radiologically improvements in magnetic resonance imaging has improved our ability to delineate patterns of injury and thereby, aid in prognosis^[47]. Piglet models of phosphorous-MRS profiles within the first 2 h post-injury can predict the evolution of injury severity^[48].

Blood biomarkers have also shown promise in predicting injury severity and outcome. Although no definitive blood biomarker has entered into routine clinical use, there are a number which have shown promise based on pilot work in small cohorts. Protein markers, such as UCH-L1, IL-6 and IL-16 and Activin A are altered significantly in cord bloods taken at birth from infants with HIE^[49-51]. In addition GFAP and S100B have shown elevations slightly later, reaching a peak at 24 h^[49,52]. Animal and, more recently, human studies have shown significant alterations in the metabolomic profile of infants with HIE^[53-55]. Transcriptomics has also shown promise in differentiating infants with perinatal asphyxia and HIE^[56]. Some evidence is also available showing that circulating microRNAs in maternal blood may be useful for the detection of hypoxia in the intrapartum period^[57]. Other bodily fluids such as urine and CSF have also been the subject of biomarker discovery work^[58]. A previous meta-analysis by Ramaswamy *et al*^[59] in this area reported cerebrospinal fluid neuron-specific enolase and IL-1 β to be a potential markers of abnormal outcome in survivors.

This list of novel biomarkers is by no means exhaustive but gives an indication of the proactive research ongoing in this rapidly emerging field. In the future one or a combination of these markers may help to offer early, rapid and reliable identification of infants suitable for neuroprotective intervention and may also provide further insight into the complex biochemical responses of the body to hypoxic-ischaemic injury.

TREATMENT OF HYPOXIC-ICHAEMIC ENCEPHALOPATHY

Based on substantial evidence from multiple randomized controlled trials, therapeutic hypothermia is now standard of care for infants with moderate and severe HIE in the majority of neonatal units where the necessary resources

are available^[14,15,60-62]. Indications for treatment vary somewhat between centres but usually involve some combination of biochemical and clinical evidence of perinatal asphyxia with overt clinical manifestations of encephalopathy often based on the recruitment criteria of the larger trials of therapeutic hypothermia^[60,61].

Unfortunately, using these current standard clinical markers, it is estimated that approximately 15%-20% of infants are mis-classified as having either a mild or no encephalopathy and are therefore not offered therapeutic hypothermia, worsening their long term prognosis^[63].

OUTCOME IN PERINATAL ASPHYXIA

The majority of infants who require significant resuscitation at birth recover quickly and have no signs of encephalopathy. These children, in general have a normal outcome and function in line with their peers academically^[64]. For this reason, at present, neuroprotective intervention has been reserved for infants with moderate or severe HIE as outlined above. However, several large population based studies now suggest that outcome in children with perinatal asphyxia without clinical encephalopathy is not completely normal. Odd *et al*^[65] demonstrated an increased risk of low IQ at 8 years in this group compared to a control group. This is concerning due to the potential risk of a huge burden of more subtle disability (Table 2).

SHORT TERM OUTCOME IN HIE

For those infants who develop HIE, the most commonly used grading system remains the Sarnat score, with infants graded as mild, moderate or severe depending on their clinical signs^[66]. The approximate breakdown tends to be mild (39%), moderate (39%) and severe (22%)^[7]. The management and outcome varies significantly with grade of HIE.

Of those with moderate HIE, approximately one third will develop clinical and electrographic seizures in the neonatal period^[39]. These seizures will usually commence between 18 and 20 h following delivery and will last for minutes to hours^[67]. Following the cessation of seizures the encephalopathy may gradually improve to the point where oral feeding can recommence and care normalised. Both seizure burden and the time to achieve full oral feeding are useful in predicting the long term outcome of the infant^[39,41]. The overall death rate in NE of all grades is 9.9% in developed countries but this rises acutely to 30% among those who qualify for cooling and precipitously to 76.8% when we consider severe encephalopathy alone^[7,14].

LONG TERM OUTCOME IN HIE

Prior to the cooling era approximately 26.4% of infants with NE survived with moderate to severe neurodevelopmental impairment and a further 14% survived with mild impairment. Reported rates of cerebral palsy following NE vary but are generally around 10%-13% among survivors

Table 2 Outcomes in perinatal asphyxia

Short-term	
Death	
HIE	
Seizures	
Long-term	
Motor	Cerebral palsy
Sensory	Hearing loss
	Visual impairment
Cognitive	Episodic and working memory
	Attention
Educational	Increased support requirements
	Lower test scores
Behavioural	Attention
	Explosiveness
	Irritability
Neuropsychiatric	Psychotic symptoms
Neurodevelopmental	Autistic spectrum

A summary table of reported outcomes in perinatal asphyxia and hypoxic-ischaemic encephalopathy; HIE: Hypoxic-ischaemic encephalopathy.

of moderate to severe encephalopathy^[68,69]. The risk is increased threefold where there is a history of neonatal seizures^[68]. Dyskinetic CP and spastic quadriplegia are the most common subtypes with 80% of dyskinetic CP attributable to perinatal hypoxia-ischaemia at term^[69]. Sensory disruption is also increased following hypoxic-ischaemic injuries. Rates of hearing loss are reported to be as high as 17.1% in those with other persistent neurological deficits^[70]. Up to 41% of infants with a diagnosis of NE have an abnormality in some element of visual function in the first year of life, and where associated with moderate to severe basal ganglia changes and severe white matter changes on MRI this rises to 100%^[71].

Therapeutic hypothermia has improved the outlook for infants with moderate to severe HIE, with increased likelihood of survival with normal IQ (RR = 1.31) and improved survival without neurological abnormalities (RR = 1.6) following therapeutic hypothermia at follow-up at 6-7 years of life^[14].

It is important to note that learning deficits may be present with or without motor or sensory dysfunction. Impairments in episodic memory associated with reduced hippocampal volume has been found in children following perinatal hypoxic-ischaemic injury but without associated neurological deficits^[72]. Robertson and Finer showed a reduction in school readiness scores as well as attention scores and increases in symptoms of explosiveness and irritability at 5.5 years in survivors of moderate encephalopathy without other disability^[73]. Marlow *et al*^[74] also demonstrated memory and attention/executive function impairments in the severe encephalopathy group and increased special educational needs and lower achievement on national curriculum attainment scores in both moderate and severe groups at 7 years^[74]. Odd *et al*^[64] have shown that infants with encephalopathy had lower working memory, reading accuracy and comprehension scores and increased requirement for educational support (OR = 6.24) between 8 and 11

years. A Swedish population based study examining the long term outcome following moderate encephalopathy has shown that in late adolescence the rates of disability are even higher, with 30% having CP, and 70% of those without CP having cognitive disability which interfered with their daily life^[75].

NE has also been associated with increased behavioural difficulties. Those children with a history of moderate and severe encephalopathy have a significant increase in parent and teacher reported hyperactivity^[74]. There is also a reported increase in autistic spectrum disorders in these children by 5 years (RR = 5.9)^[76]. Adverse perinatal events are also associated with an increased risk of psychotic symptoms including schizophrenia^[77,78].

The longer we follow these children the more evident it becomes that perinatal asphyxia and HIE have significant long term non-motor effects.

CONCLUSION

It is important to end with the note that the statistics quoted thus far have predominantly focused on high income countries, where research is most active. However, the greatest burden of disease is in low and middle income countries. Worldwide 10 million infants a year will suffer perinatal respiratory depression, of which 1.15 million will develop clinical encephalopathy. In countries with low neonatal mortality rates (NMR < 5) the incidence of NE is 1.6 per 1000 births rising to 12.1 per 1000 deliveries in countries with high NMR (> 15)^[7]. It is estimated that 23% of neonatal deaths worldwide can be attributed to asphyxia which equates to nearly 1 million neonatal deaths per year; and in a countries with high neonatal mortality rates the death rate is 8 times that of countries with low NMRs^[79]. Lack of modern obstetric care, inadequate neonatal resuscitation and lack of therapeutic hypothermia will cause this gap to widen. We need to strive for effective, reliable and inexpensive measures to enable early identification of infants at risk of long term injury, where low cost interventions, such as cooling, are potentially feasible and can produce significant and lifelong improvements on quality of life for these children, their parents and their communities^[80].

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