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Perinatal Asphyxia and Hypoxic Ischemic Encephalopathy – The Current Situation

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INTRODUCTION

Complications during delivery can lead to poor neonatal outcomes in otherwise normal fetuses. Perinatal asphyxia (PA) is an important cause of death and disability related to events during birth and results from compromised placental or pulmonary gas exchange. This can lead to hypoxia and hypercarbia resulting in anaerobic glycolysis and acidosis causing severe metabolic challenges, even when the insult doesn't lead to fatal outcome[1]. Following PA, systemic hypoxia-ischemia results in multi-organ dysfunction, but the most significant long lasting effects are evident in cerebral function of affected infants. The resulting condition caused by the hypoxic ischemic insult to the brain is termed Hypoxic Ischaemic Encephalopathy (HIE). Cerebral hypoxia-ischemia remains a major cause of acute perinatal brain injury, leading to severe neurodevelopmental impairments. Despite improvements in perinatal care PA still occurs[2,3] with an incidence of 2–6/1000 term births in developed countries[4], reaching higher rates in developing countries[5,6] Though some cases of asphyxia are preventable, the ability to predict those fetuses at risk remains poor[7].

CAUSES AND RISK FACTORS

Intrapartum events such as placental abruption, umbilical cord prolapse and uterine rupture accounts for majority of cases (56-80%)[8,9]. Intrapartum disturbance usually in association with an antenatal risk factor, such as diabetes mellitus, preeclampsia, or intrauterine growth restriction (IUGR) occurs in 10 to 35% of cases of PA[7]. Placental insufficiency will contribute to 10% of cases of PA. Intra-amniotic infection and prolonged or difficult deliveries also associated with an increased risk of PA[10], encephalopathy and cerebral palsy[11,12]. Postnatal insult occurs only in 10% of cases of PA, due to prematurity severe cardiopulmonary abnormalities such as congenital heart disease, persistent pulmonary hypertension of the newborn or severe circulatory insufficiency[13]. These catastrophic events are usually not preventable and sometimes may not be predictable[14].

However, the timing of injury often is difficult to establish for an individual infant, in part because antepartum and intrapartum events may not lead to signs that are detectable in the fetus. In addition, a fetus who has suffered an antepartum insult may be at increased risk of incurring further intrapartum injury[15].

ANTEPARTUM SCREENING AND DIAGNOSIS

Fetal movement counting

Even though, fetal movements decreases in response to hypoxemia, making formalized maternal assessment of fetal movements is a potentially simple method of monitoring fetal oxygenation and well-being. A recent systematic review concluded that there is insufficient evidence to recommend routine fetal movement to reduce PA[16] .

CST, NST, biophysical properties (BPP) and modified BPP

The contraction stress test (CST) is based on the promise that uterine contractions transiently restrict oxygen delivery to the fetus and that a hypoxic fetus will demonstrate recurrent late decelerations. Drawbacks to the CST include the need to stimulate contractions and the fact that inducing contractions is contraindicated in a number of conditions (e.g. placenta previa)[17]. CST is replaced by a less intensive method, the non stress test (NST), combined with real-time ultrasonography. When normal, these tests are highly reassuring with a low false-negative rate.

The biophysical profile (BPP) combines the ultrasonographic estimation of Amniotic fluid volume (AFV) and assessments of fetal breathing, gross body movements and the NST[18]. This test is felt to assess indicators of both acute (NST, breathing, body movement) and chronic (AFV) hypoxia, and the BPP score is linearly correlated with fetal pH[19].

Recent evidence suggests that Doppler evaluation of fetal veins combined with arterial assessments is useful for predicting PA in growth-restricted fetuses[20].

INTRAPARTUM MONITORING

Although, there is insufficient scientific evidence to demonstrate, that any form of intrapartum fetal monitoring including cardiotochography, fetal blood sampling, fetal PH monitoring lactate measurement, fetal pulse oximeter and ST waveform analysis improves clinical outcome, several centres have reported a reductions in HIE and intrapartum death rates[21,22].

DIAGNOSIS OF PA IN THE NEONATE

The American Academy of Paediatrics (AAP) and the American College of Obstetrics and Gynaecologist (ACOG) have the following essential criteria to diagnose PA[23].

I. profound metabolic or mixed acidemia (pH <7.0 in an umbilical arterial blood at birth)

II. persistence of an Apgar score of 0–3 for longer than 5 min

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III. neonatal neurologic sequelae (e.g. seizures, coma, hypotonia),

IV. multiple organ involvement (e.g. kidney, lungs, liver, heart, intestines)

A widely used clinical classification of HIE devised by Sarnat & Sarnat (1976) classifies HIE into 3 stages, according to the conscious level, neurological and autonomic parameters and collates these with electroencephalographic (EEG) findings in the baby[24];

1. Mild (stage I)- characterized by hyper alertness, uninhibited Moro and stretch reflexes, sympathetic effects, and a normal EEG
2. Moderate (stage II)- infant has obtundation, hypotonia, strong distal flexion, and multifocal seizures. The EEG shows a periodic pattern sometimes preceded by continuous delta activity.
3. Severe- stage 3 – infant is stuporous and flaccid, with suppressed brain stem and autonomic functions. The EEG is iso-potential or has infrequent periodic discharges.

HIE is known to cause a wide spectrum of long-term neurological and psychiatric outcomes. Severe HIE causes cerebral palsy, mental retardation and epilepsy[25]. Mild to moderate asphyxia has been associated with cognitive and behavioral disorders such as low IQ, hyperactivity, autism and attention deficits in children and adolescents. There has also been an increased incidence of schizophrenia and psychotic disorders in adulthood in affected infants[25].

MARKERS OF PA

Since early intervention minimizes or prevents long-term adverse neurological outcome, much effort has been directed towards identifying early markers of PA. There is no single serological marker predictive of HIE. The number of Nucleated RBC (NRBC) count and NRBC count per 100 white blood cells (NRBC/100WBCs) have been found to be higher in patients developing HIE grade III[26]. Serum lactate dehydrogenase [LDH] was also found to be a good predictor of HIE during the first 12 hours after birth[27,28]. These results offer potential inexpensive prognostic markers in newborn infants with perinatal asphyxia.

Other markers include serum levels of creatine kinase – Brain Band (CK-BB) and Interleukin-6 which show a correlation with the severity of HIE and its long-term outcome. Elevated levels of CK-BB show an early positive correlation (as early as 2 hours after birth), with the severity of asphyxia[26]. However these markers are not routinely available in resource-restricted settings, where PA is more prevalent.

EEG MONITORING

EEG is a simple bedside investigation which usefully correlates with the broad outcome of HIE. While a normal EEG denotes normal outcome, and EEG with burst suppression indicates death or a pathological outcome in affected infants[26]. Amplified integrated EEG (a EEG) – a continuous bedside monitoring of single channel EEG - recorded during the first 72 hours after birth, also had a strong predictive value in infants with HIE[29].

IMAGING STUDIES

Cranial ultrasound is a simple, freely available investigation which can be used to identify changes of HIE, but it is not very useful in the early stages. Magnetic Resonance Imaging (MRI) is the most useful since it shows specific changes as early as 4th day of HIE, and hence could be used as an early prognostic tool26.

Changes in MRI performed during the second week of life can be used as a prognostic indicator for long-term outcome in affected neonates[30].

TREATMENT MODALITIES

Therapeutic hypothermia (TH) is a process of controlled cooling of head or whole body, used as a method of neuroportection in conditions of severe insults to the brain. During the last decade, TH has become established as the standard treatment method for infants with moderate or severe HIE born after 35 weeks of gestation.

Current treatment protocols for TH consist of slow controlled head or body cooling. TH is essentially commenced within the first 6 hours of life, with cooling to either 34.5 ± 0.5°C (for head cooling) or 33.5 ± 0.5°C (for whole-body cooling) and continued for 48–72 hours[31].

Meta analyses from RTC shows a definite beneficial effect of TH for infants with moderate and severe HIE, specially when treatment is commenced within the first six hours of life[32] However, its efficacy and safety in infants less than 35 weeks of gestation is yet to be established[35]. Adverse effects observed with TH were infrequent in the target temperature ranges and time limits used – 33.5°C to 34.5°C, up to 72 hours[32]. The most common were sinus bradycardia and prolongation of the QT interval on ECG - both physiological responses to hypothermia. Rare effects included reddening or hardening of the skin (in systemic hypothermia) and of the scalp (in head cooling), and subcutaneous fat necrosis. Significant thrombocytopenia (platelet count <150 000/mm^3) occurred in some patients[32].

COMBINED THERAPY

Improved neuro protection has been reported when TH was combined with anticonvulsant or anti-excitatory drugs including phenobarbital[33,34], topiramate and levetiracetam[35,36]. A phase III clinical trail on the adjuvant effect of Magnesium sulphate on TH (which has been recently concluded) is also showing important evidence to this effect, while erythropoetein, and Stem Cell transplants show promising results in a few ongoing clinical trials[26,37].

CONCLUSION

Perinatal asphyxia will result in neonatal hypoxia and tissue/organ injury. A variety of maternal, obstetric, and neonatal conditions predispose the fetus and newborn to asphyxia, which can occur before, during or after birth. One of the most effective ways to reduce the risk is vigilance of at-risk pregnancies and appropriate timely intervention. It is important to develop intra partum fetal monitoring techniques and to assure that health-care professionals have an easier access even though many of these techniques is controversial and the ability to detect fetal compromise is often unknown.

In the last decade, significant progress has been made in the treatment of infants affected with HIE. Therapeutic Hypothermia has emerged as the most useful treatment option in the last decade and more extensive research needs to be done to fine tune its therapeutic option and their applicability in pre term infants.

Early clinical trials with other adjuvant therapies such as anticonvulsants, antioxidants and anti-inflammatory drugs have also proven to be of use. Other interventions such as brain Stem cell transplantation, and the use of Insulin like GF and erythropoietin are also showing promising results in ongoing trials.

Although PA is hypothetically preventable, as clinicians we realize that this is not so in real life situations. Therefore, it is heartening to know that successful therapeutic options are available for affected infants. However, the main treatment options are still at a relatively early stage and further urgent research is needed to maximize benefits of these options.

REFERENCES

1. Herrera-Marschitz M, Morales P, Leyton L, Bustamante D, Klawitter V, Espina-Marchant P, et al. Perinatal asphyxia: current status and approaches towards neuroprotective strategies, with focus on sentinel proteins. Neurotox Res. 2011;19:603–27.
2. Berger R, Garnier Y. Perinatal brain injury. J Perinat Med. 2000;28:261–85.
3. Vannucci SJ, Hagberg H. Hypoxia-ischemia in the immature brain. J Exp Biol. 2004; 207:3149–54.
4. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010; 86:329–38.
5. Lawn JE, Kerber K, Enweronu-Laryea C, Cousens S. 3.6 million neonatal deaths what is progressing and what is not? Semin Perinatol. 2010; 34:371–86.
6. Wall SN, Lee AC, Carlo W, Goldenberg R, Niermeyer S, Darmstadt GL, et al. Reducing intrapartum-related neonatal deaths in low- and middle-income countries-what works? Semin Perinatol. 2010; 34:395–407.
7. Grimes DA, Peipert JF. Electronic fetal monitoring as a public health screening program: the arithmetic of failure. Obstet Gynecol 2010; 116(6):1397–400.
8. Nelson DB, Lucke AM, McIntire DD, et al. Obstetric antecedents to body-cooling treatment of the newborn infant. Am J Obstet Gynecol 2014; 211(2):155.e1–6.
9. Wayock CP, Meserole RL, Saria S, et al. Perinatal risk factors for severe injury in neonates treated with whole-body hypothermia for encephalopathy. Am J Obstet Gynecol 2014; 211(1):41.e1–8.
10. MacKenzie IZ, Shah M, Lean K, et al. Management of shoulder dystocia: trends in incidence and maternal and neonatal morbidity. Obstet Gynecol 2007; 110(5): 1059–68.
11. Blume HK, Li CI, Loch CM, et al. Intrapartum fever and chorioamnionitis as risks for encephalopathy in term newborns: a case-control study. Dev Med Child Neu- rol 2008; 50(1): 19–24.
12. Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. JAMA 1997; 278(3): 207–11.
13. Volpe JJ. Perinatal brain injury: from pathogenesis to neuro- protection. Ment Retard Dev Disabil Res Rev. 2001; 7:56–64.6
14. Christina AH, Robert MS Perinatal Asphyxia from the Obstetric Standpoint Diagnosis and Interventions Clin Perinatol 43 (2016) 423–438.
15. Volpe JJ. Hypoxic-ischemic encephalopathy: Clinical aspects. In: Neurology of the Newborn, 5th ed, Saunders Elsevier, Philadelphia 2008. p.400.
16. Practice bulletin no. 145: antepartum fetal surveillance. Obstet Gynecol 2014; 124(1): 182–92.
17. Caroline S, Roger KF, Catherine YS Antenatal Testing – A Reevaluation Executive Summary of a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Workshop Obstet Gynecol. 2009 Mar; 113(3): 687–701.
18. Manning FA, Snijders R, Harman CR, Nicolaides K, Menticoglou S, Morrison I. Fetal biophysical profile score. VI. Correlation with antepartum umbilical venous fetal pH. IS J Obstet Gynecol. 1993; 169:755–63. [PubMed]
19. Manning FA, Snijders R, Harman CR, Nicolaides K, Menticoglou S, Morrison I. Fetal biophysical profile score. VI. Correlation with antepartum umbilical venous fetal pH. Am J Obstet Gynecol. 1993;169:755–63.
20. Kiserud T, Kessler J, Ebbing C, Rasmussen S. Ductus venosus shunting in growth-restricted fetuses and the effect of umbilical circulatory compromise. Ultrasound Obstet Gynecol. 2006; 28:143–9. [PubMed]
21. Byford S, Weaver E, Anstey C. Has the incidence of hypoxic ischaemic encephalopathy in Queensland been reduced with improved education in fetal surveillance monitoring? Aust N Z J Obstet Gynaecol 2014; 54(4):348e53.
22. Walsh CA, McMenamin MB, Foley ME, et al. Trends in intrapartum fetal death, 1979-2003. Am J Obstet Gynecol 2008; 198(1): 47. e1e7.
23. American College of Obstetrics and Gynecology., Task Force on Neonatal Encephalopathy and Cerebral Palsy., American Academy of Pediatrics. Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology. Edited by Washington, DC, American College of Obstetricians and Gynecologists, 2003.
24. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976; 33:696–*705.*
25. Paola Morales & Diego Bustamante & Pablo Espina-Marchant & Tanya Neira-Peña & Manuel A. Gutiérrez-Hernández & Camilo Allende-Castro & Edgardo Rojas-Mancilla; *Pathophysiology of perinatal asphyxia: can we predict and improve individual outcomes?* EPMA Journal (2011) 2:211–230
26. Roberto Antonucci1, Annalisa Porcella1, Maria Dolores Pilloni, *Perinatal asphyxia in the term newborn;* Journal of Pediatric and Neonatal Individualized Medicine 2014; 3(2):e030269.

27. Mathias Karlsson (mathias.karlsson@ki.se)1,2, Eva Wiberg-Itzel1 , Ela Chakkarapani4 , Mats Blennow3 , Birger Winbladh1 , Marianne Thoresen *Lactate dehydrogenase predicts hypoxic ischaemic encephalopathy in newborn infants: a preliminary study;* 2010 The Author(s)/Journal Compilation ª2010 Foundation Acta Pediatric/Acta Paediatrica

28. *Evaluation of Serum Creatine Kinase Muscle-Brain Fraction (CK-MB) and Lactate Dehydrogenase (LDH) as Markers of Perinatal Asphyxia in Term Neonates* Masaraddi Sanjay K1* , Sarasu M2 , Sulekha C 3 , Vijayalakshmi M4 Int J Med Health Sci. July 2014,Vol-3;Issue-3

29. DelInt J Med Health Sci. July 2014,Vol-3;Issue-3 Río R1, Ochoa C2, Alarcon A1, 3, Arnáez J4, Blanco D5, García-Alix Pubmed : PLoS 1: 2016 Nov 1; 11(11): e0165744. doi: 10.1371/journal.pone.0165744. e-Collection 2016.

30. Agut T1, León M, Rebollo M, Muchart J, Arca G, Garcia-Alix A. *Early identification of brain injury in infants with hypoxic ischemic encephalopathy at high risk for severe impairments: accuracy of MRI performed in the first days of life.* BMC Pediatr. 2014 Jul 8; 14:177.

31. A1.Joanne O. Davidson, [1] Guido Wassink, [1] Lotte G. van den Heuij, [1] Laura Bennet, [1] and Alistair J. Gunn *Therapeutic Hypothermia for Neonatal Hypoxic–Ischemic Encephalopathy – Where to from Here?* Frontiers of neurology; Published online 2015 Sep 14. doi: 10.3389/fneur.2015.00198

32. Paeditrics 2014: vol 133/issue 6- from the American Academy of Pediatrics) Clinical Report ; Hypothermia and Neonatal Encephalopathy -committee on fetus and newborn.

33. Meyn Jr DF, Ness J, Ambalavanan N, Carlo WA. Prophylactic phenobarbital and whole-body cooling for neonatal encephalopathy. J Pediatr. 2010; 157:334–6.

34. Barks JD, Liu YQ, Shangguan Y, Silverstein FS. Phenobarbital augments hypothermic neuroprotection. Pediatr Res. 2010; 67:532–7.

35. Filippi L, Poggi C, la Marca G, Furlanetto S, Fiorini P, Cavallaro G, et al. Oral topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia: a safety study. J Pediatr. 2010; 157:361–6

36. Cilio MR, Ferriero DM. Synergistic neuroprotective therapies with hypothermia. Semin Fetal Neonatal Med. 2010; 15:293–

37. https://clinicaltrials.gov/ct2/show/NCT02499393- accessed 8 March 2017