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BLOOD BIOMARKERS FOR EVALUATION OF PERINATAL ENCEPHALOPATHY- STATE OF THE ART

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Abstract

Purpose of the review—The rapid progress in biomarker science is on the threshold of significantly changing clinical care for infants in the Neonatal Intensive Care Unit. Infants with neonatal brain injuries will likely be the first group whose management is dramatically altered with point-of-care, rapidly available brain biomarker analysis. Providing an interim update on progress in this area is the purpose of this review.

Recent Findings—Highlighted findings from the past 18 months of publications on biomarkers in neonatal brain injury include; i) Specific non-brain markers of cardiac health and global asphyxia continue to provide information on brain injury after HIE. ii) Prediction of injury in the piglet HI model is improved with the use of a combination score of plasma metabolites. iii) In a neonatal piglet model of perinatal hypoxia-ischemia, a systemic pro-inflammatory surge of cytokines has been identified after rewarming from therapeutic hypothermia. iv) New biomarkers identified recently include osteopontin, activin A, neutrophil gelatinase-associated lipocalin (NGAL), secretoneurin, Tau, and neurofilament light protein. v) Brain based biomarkers differ in their ability to predict short term in-hospital outcomes and long term neurologic deficits.

Summary—Neonatal brain biomarker research is currently in its very early development with major advances still to be made.

Keywords

Neonatal brain injury; Metabolites; Outcomes; Cytokines; Digital ELISA

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Conflicts of interest

AE is a consultant to Immunarray, Inc.

Introduction

Hypothermia is currently the only recognized standard of care treatment for moderate to severe perinatal hypoxic-ischemic encephalopathy (HIE), but about 45% of neonates have abnormal outcomes despite treatment.[1] Management of neonates with hypoxic-ischemic encephalopathy (HIE) is hindered by the lack of quantifiable biomarkers that could measure the degree of injury, assist in triage to therapy and give prognostic information. Currently the diagnosis and prognosis of HIE in a neonate is based on clinical manifestations, imaging and electrophysiological monitoring.[2] MRI biomarkers for HIE have generally been performed several days following birth because of the lack of early sensitivity for hypoxic injury, and MRI requires that the infant be moved from the NICU to the imaging suite, a task that can be difficult under certain circumstances. Both of these can be overcome with the use of head ultrasound (HUS) as an imaging biomarker [3*]; however, HUS is not well tested nor universally accepted for this purpose because of lower sensitivity.[4*] Biochemical evaluation of the severity of birth asphyxia has traditionally been performed using umbilical arterial blood gases at birth, but this test is poorly predictive of injury. Taken together, these constraints make long term neurodevelopmental outcome difficult to predict in the first few days of life. Multi-organ involvement, although common when brain injury occurs, is not part of the diagnosis of HIE. In the presence of HIE the most frequently injured organs are the heart, liver, kidneys and hematological system which may release organ specific biomarkers into the blood which will have a role in the assessment of injury severity and long term outcome.[5*] While new single biomarker studies continue to emerge, biomarker science is also utilizing metabolomic profiling to more comprehensively understand the effects of injury and treatment on entire pathways following neonatal brain injury [6**] and may likely unveil new therapeutic targets. The measurement of quantitative biomarkers that are able to detect subclinical lesions at a stage when routine brain monitoring or imaging is still silent would be a major advance in the care of neonates with suspected brain injury.[5*] Biomarkers could allow the screening of neonates for brain injury with high sensitivity and specificity, monitor the progression of injury and response to therapy through serial measurements due to their short half-life and correlate with the extent of brain lesions later seen on ultrasound or MRI.[5*]

Other detailed reviews are available for brain biomarkers and some are specific to the neonatal brain.[7*, 8*] This review is meant to update very recent data on biochemical biomarkers related to hypoxic-ischemic brain injury in the newborn.

Biomarkers for Other Conditions Now Being Applied to HIE

A number of biomarkers used to identify other conditions are now being used to identify neonatal neurologic injury. Cardiac biomarkers show good correlation with echo-derived markers of myocardial function, and a significant elevation of cord blood troponin has been found to be an excellent early predictor of severity of HIE and mortality in term infants.[9**] Dickkopf-1 is a regulatory antagonist in the Wnt family of glycoproteins which are involved in the signaling of embryonic development and numerous diseases.[10*] Dickkopf-1 is one of several mediators that are released from platelets on activation, and is involved in platelet-mediated endothelial activation in patients with coronary artery disease.

It is elevated in patients with stable and unstable angina pectoris. A study of 20 neonates with HIE compared to 20 controls found that Dickkopf-1 was released into the circulation of neonates with HIE and correlated with HIE severity which may allow it to be useful for prognosis.[10*] It appears from this report that therapeutic hypothermia was not used in the treatment of these infants thus cardiac depression from cooling should not have interfered with the interpretation. Phenobarbital was used liberally, however there is no analysis for this as a confounder.

Post hoc analysis of glycemic control in 234 neonates with moderate to severe HIE from the CoolCap study showed that both hypoglycemia and hyperglycemia were independently associated with unfavorable outcome. Any glucose derangement during the early postnatal period in infants with moderate-to-severe HIE was independently associated with an unfavorable outcome at 18 months, independent of severity of HIE and cooling therapy.[11] Lactate dehydrogenase (LDH), an enzyme that exists in all cells and is released into the plasma by cellular damage, has been investigated as an inexpensive and safe prognostic biomarker in neonates with HIE.[12*] A study of 92 neonates with HIE found that although LDH levels did not differ for those with brain lesions on MRI, the change in LDH was significantly higher on day 3 of life in neonates with central gray matter lesions, which led these investigators to claim that changes in serum LDH may be a useful biomarker for predicting future neurodevelopmental prognosis in infants with HIE.[12*]

Metabolic Profiling of Neonatal HIE

When mass spectrometry was applied to provide metabolic profiles of brain tissue and plasma following an excitotoxic lesion to the neonatal mouse brain it was found that a short list of amino acids and glycerophospholipids explained the effects of the excitotoxic lesion.[13**] These investigators concluded that these targets may be useful starting points for studies on acute and tertiary phase biomarkers specific to the excitotoxic processes. [13**] In a newborn piglet model of HIE, time-dependent metabolic biomarker profiles of choline, betaine, cytidine and uridine were observed to have patterns similar to lactate levels, which are currently considered the gold standard for assessing hypoxia, and they concluded that the prediction of injury could be improved with the use of a combination of plasma metabolites.[14**] A metabolite score calculated based on the relative intensities of 3 metabolites (choline, 6,8-dihydroxypurine and hypoxanthine) was compared to lactate as a biomarker for the intensity and duration of perinatal hypoxia in a neonatal piglet model.[15**] For plasma samples drawn before and directly after a hypoxic insult the metabolite score performed similar to lactate, but it provided better predictive capacity at 2 hours after resuscitation. Serial determinations of such a score in a minimally invasive bio-fluid may improve the early assessment of the severity of the hypoxic insult and assist in the diagnosis and triage to treatment.[15**] In a nonhuman primate model using in utero umbilical cord occlusion to induce HIE, 63 metabolites were examined as potential biomarkers of brain injury. Of this group, 8 (arachidonic acid, botanic acid, citric acid, fumaric acid, lactate, maleate propanoic acid and succinic acid) were identified that correlated with early and/or long-term neurodevelopmental outcomes.[16] When hypoxia and hypotension were induced in newborn piglets, the plasma metabolome showed an increased plasma concentration of analytes reflecting a metabolic adaptation to prolonged anaerobiosis; however, after

resuscitation metabolite levels returned to the starting values.[17*] Choline was the most significantly increased analyte during the hypoxic insult, and they concluded that these metabolites could have applicability in predicting the severity of hypoxia in the clinical setting. [17*]

Inflammatory Biomarkers of HIE

Cytokine and chemokine levels may be specific to the phase of injury and recovery, switching roles within a relatively short time after hypoxia-ischemia.[18*] A study in a neonatal piglet model of perinatal hypoxia-ischemia demonstrated a systemic pro-inflammatory surge after rewarming in the hypothermia group, which is counterintuitive to the theorized neuroprotective effects of hypothermia.[18*] The authors speculated that the role of cytokines during and after cooling may change and that hypothermia should be complemented with anti-inflammatory therapies for maximal benefit.[18*] In a study of 30 term newborn infants with birth asphyxia, proinflammatory cytokines, neuron specific enolase and S-100 were found to be significantly elevated in cord blood.[19*] Activation of glial cells caused by hypoxic-ischemic oxygen deprivation is associated with the release of inflammatory mediators, including IL-6, TNF-α, IL-1α, IL-1β, interferon-γ and reactive oxygen species.[19*] Whether these results are causal has not been determined from these studies, and they may in fact present new therapeutic targets or may be the result of secondary injuries following the primary insult.

A prospective randomized pilot study of newborns delivered after >36 weeks to selective head cooling or whole body cooling found that the effects on biomarkers did not differ. They also found that serum IL-6 levels may be useful for predicting disability and mortality in newborns with HIE.[20]

New Biomarkers for HIE

Recent studies have identified a number of biomarkers that may improve identification of neonatal neurologic injury in the period shortly after birth. Studies in 10 day old mice reveal that HI significantly increases osteopontin, a finding not observed after LPS administration.[21*] Osteopontin mRNA was induced in the brain but not in the blood, and immunostaining revealed osteopontin expression by microglia/macrophages in the HI-injured brain. They concluded that osteopontin may be a prognostic blood biomarker in HIE related to brain microglial activation, and that an increase of plasma osteopontin may indicate a perinatal event at least 24 hours old. Therefore, it might be useful as a marker of prior intrauterine HI stress and a poorer response to hypothermia treatment.[21*] Analysis of umbilical cord blood from 24 term neonates with perinatal hypoxia revealed a significant increase in activin A and neutrophil gelatinase-associated lipocalin (NGAL) compared to 34 healthy controls, with NGAL being a better marker of perinatal hypoxia.[22*] In adults suffering from brain injury, secretoneurin is a promising early biomarker of poor outcome. Elevated levels of secretoneurin were similarly noted in cord blood from neonates with HIE following perinatal asphyxia.[23*] Tau and neurofilament light protein levels are significantly elevated in cord blood after moderate-severe HIE and correlate with the severity of the insult.[24*] Ubiquitin

C-terminal hydrolase-L1 (UCH-L1), measured in the serum, is another potential prognostic biomarker for various forms of CNS injury, including neonatal HIE.[25, 26*]

Oxidative stress is a crucial step in the development of HIE and biomarkers such as lipid peroxidation products have been found to be increased in cord blood at delivery with severe metabolic acidosis.[27**] Selenium is a constituent of the antioxidant enzyme glutathione peroxidase and is vital to antioxidant defense. Neonates with HIE have been found to have lower serum selenium levels than normal healthy neonates, independent of maternal levels, and selenium levels were negatively correlated with the severity of HIE.[28]

New Technologies in Biomarker Detection

The development of novel methodologies to detect brain injury proteins with improved sensitivity and speed may provide results that are clinically actionable. Breakthroughs in digital ELISA assays such as the Simoa platform (Quanterix, Lexington, MA) allow femptogram/microliter detection of brain proteins such as Tau.[29] Advances are also being made in developing rapid detection biosensor platforms that may enable bedside detection of brain injury proteins. Organic field effect transistors have already demonstrated < 3 minute detection of GFAP. [30, 31] Alternatively, silicon nanowires coated with detection antibodies also have the potential for protein detection within two minutes.[32] These platforms have the potential to revolutionize how we care for neonatal brain injury.

Neurodevelopmental Follow-up for Previously Studied Brain Injury Biomarkers

Only recently have studies evaluated neurodevelopmental follow-up associated with biomarkers found to be associated with neonatal brain injury during the perinatal period. In neonates born at > 35 weeks with HIE, serum lactate levels measured after 72 hours of whole body hypothermia correlated with neurodevelopmental outcome at 24 months corrected age.[33] Although IL-6 and IL-16 measured in umbilical cord blood at birth were correlated with HIE severity, IL-6 did not show any association with outcome at the age of 3 years.[34*]. IL-16 levels at birth were predictive of severe deficits, especially when used in combination with electroencephalogram findings.[34*]

Prior studies have shown Glial Fibrillary Acidic Protein (GFAP) measured in neonatal blood at 1–2 and 4–7 days of life (but not in cord blood) were associated with abnormal brain MRI at 7–10 days of life.[35]. Furthermore, GFAP levels at time of NCU admission were significantly higher in those infants with feeding abnormalities at time of NICU discharge. [35] Chalak et al also demonstrated that GFAP in neonates with moderate to severe HIE was elevated at birth and associated with abnormal neurologic outcomes.[36] Looney et al, utilizing a different laboratory assay, noted that GFAP measured in cord blood at birth was not increased in those with brain injury compared to healthy controls, and no correlation was found between cord blood levels of GFAP and outcome at 36 months.[37] These data point out the potential exquisite time dependence of the biomarker in relation to time of injury.

Conclusion

Given the variation of causes and symptoms at presentation of neonatal HIE, it is unlikely that a single early biomarker will be able to predict clinical outcomes in the perinatal period. [8*, 15**] A panel of multiple inflammatory and neuronal biomarkers measured via a point of care bedside tool at various time points is likely to be the most accurate way to identify, and assess the severity, timing and pattern of injury. Furthermore, full pathway analysis via various –omic strategies may identify new therapeutic targets for neonatal HI brain injury. Neonatal brain biomarker research is currently in its very early development with major advances still to be made.

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References

1. Shankaran S, Pappas A, McDonald S, Vohr B, Hintz S, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. The New England journal of medicine. 2012; 366(22): 2085–92. [PubMed: 22646631]
2. Lv H, Wang Q, Wu S, Yang L, Ren P, Yang Y, et al. Neonatal hypoxic ischemic encephalopathy-related biomarkers in serum and cerebrospinal fluid. Clin Chim Acta. 2015; 450:282–97. [PubMed: 26320853]
3*. Gerner GJ, Burton VJ, Poretti A, Bosemani T, Cristofalo E, Tekes A, et al. Transfontanellar duplex brain ultrasonography resistive indices as a prognostic tool in neonatal hypoxic-ischemic encephalopathy before and after treatment with therapeutic hypothermia. J Perinatol. 2016; 36(3):202–6. Pre- and post-cooling transfontanellar duplex brain sonographic resistive index values may be a useful prognostic tool, in conjunction with other clinical information, for neonates diagnosed with HIE. [PubMed: 26609871]
4*. Bano S, Chaudhary V, Garga UC. Neonatal Hypoxic-ischemic Encephalopathy: A Radiological Review. J Pediatr Neurosci. 2017; 12(1):1–6. This article reviews the etiopathophysiology and clinical manifestations of HIE, role of imaging in the evaluation of the condition, patterns of brain injury in term and preterm neonates, the treatment and prognosis. [PubMed: 28553370]
5*. Satriano A, Pluchinotta F, Gazzolo F, Serpero L, Gazzolo D. The potentials and limitations of neuro-biomarkers as predictors of outcome in neonates with birth asphyxia. Early Hum Dev. 2017; 105:63–7. This review reports the potentials and limitations of biomarkers in predicting outcome in neonates complicated by perinatal asphyxia. [PubMed: 27993431]
6**. Denihan NM, Kirwan JA, Walsh BH, Dunn WB, Broadhurst DI, Boylan GB, et al. Untargeted metabolomic analysis and pathway discovery in perinatal asphyxia and hypoxic-ischaemic encephalopathy. J Cereb Blood Flow Metab. 2017 271678X17726502. These investigators have identified perturbed metabolic pathways and potential biomarkers specific to perinatal asphyxia and HIE, which measured at birth, may help direct treatment.
7*. Graham EM, Burd I, Everett AD, Northington FJ. Blood Biomarkers for Evaluation of Perinatal Encephalopathy. Front Pharmacol. 2016; 7:196. This reviews quantitative serum biomarkers that could improve the precision in identifying intapartum fetal hypoxia-ischemia, the neonatal diagnosis of HIE and measure the effectiveness of treatment for HIE. [PubMed: 27468268]
8*. Chalak LF. Inflammatory Biomarkers of Birth Asphyxia. Clin Perinatol. 2016; 43(3):501–10. This review covers inflammatory serum biomarkers in the setting of birth asphyxia that can help assess the degree or severity of encephalopathy at birth and neurodevelopmental outcomes. [PubMed: 27524450]

9**. Neves AL, Henriques-Coelho T, Leite-Moreira A, Areias JC. Cardiac injury biomarkers in paediatric age: Are we there yet? Heart Fail Rev. 2016; 21(6):771–81. Significant elevation of cord troponin is an excellent early predictor of severity of HIE and mortality in term infants. [PubMed: 27255332]

10*. Albanna EA, Ahmed HS. Circulating Dickkopf-1 in hypoxic ischemic neonates. J Matern Fetal Neonatal Med. 2016; 29(13):2171–5. There is an increasing level of Dickkopf-1 released into the circulation of neonates with HIE with higher levels in severe injury. [PubMed: 26365699]

11. Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ, et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed. 2016; 101(2):F149–55. [PubMed: 26283669]

12*. Yum SK, Moon CJ, Youn YA, Sung IK. Changes in lactate dehydrogenase are associated with central gray matter lesions in newborns with hypoxic-ischemic encephalopathy. J Matern Fetal Neonatal Med. 2017; 30(10):1177–81. Changes in serum LDH may be a useful biomarker for predicting future neurodevelopmental prognosis in infants with HIE. [PubMed: 27363261]

13**. Blaise BJ, Schwendimann L, Chhor V, Degos V, Hodson MP, Dallmann G, et al. Persistently Altered Metabolic Phenotype following Perinatal Excitotoxic Brain Injury. Dev Neurosci. 2017; 39(1–4):182–91. This study demonstrates that metabolic profiling is a useful approach to identify acute and tertiary effects in an excitotoxic brain lesion model that generates a short list of biomarker targets with future potential in the hunt for identification of injury, stratifiation and possibly therapy. [PubMed: 28494460]

14**. Sanchez-Illana A, Solberg R, Lliso I, Pankratov L, Quintas G, Saugstad OD, et al. Assessment of phospholipid synthesis related biomarkers for perinatal asphyxia: a piglet study. Sci Rep. 2017; 7:40315. This study demonstrates the usefulness of choline and related metabolites for improving the early assessment of the severity of the hypoxic insult. [PubMed: 28071721]

15**. Kuligowski J, Solberg R, Sanchez-Illana A, Pankratov L, Parra-Llorca A, Quintas G, et al. Plasma metabolite score correlates with Hypoxia time in a newly born piglet model for asphyxia. Redox Biol. 2017; 12:1–7. This study shows the usefulness of the metabolite score for improving the early assessment of the severity of the hypoxic insult based on serial determinations in a minimally invasive biofluid. [PubMed: 28209514]

16. Chun PT, McPherson RJ, Marney LC, Zangeneh SZ, Parsons BA, Shojaie A, et al. Serial plasma metabolites following hypoxic-ischemic encephalopathy in a nonhuman primate model. Dev Neurosci. 2015; 37(2):161–71. [PubMed: 25765047]

17*. Solberg R, Kuligowski J, Pankratov L, Escobar J, Quintas G, Lliso I, et al. Changes of the plasma metabolome of newly born piglets subjected to postnatal hypoxia and resuscitation with air. Pediatr Res. 2016; 80(2):284–92. Severe hypoxia induces early, significant and transient changes of specific metabolites in the plasma metabolome, which represent a snapshot of the biochemical adaptation of mammals to intense hypoxia. [PubMed: 27055187]

18*. Rocha-Ferreira E, Kelen D, Faulkner S, Broad KD, Chandrasekaran M, Kerenyi A, et al. Systemic pro-inflammatory cytokine status following therapeutic hypothermia in a piglet hypoxia-ischemia model. J Neuroinflammation. 2017; 14(1):44. Following cerebral HI, there was a systemic pro-inflammatory surge after rewarming in the hypothermia group, which is counterintuitive to the putative neuroprotective effects of hypothermia. [PubMed: 28253907]

19*. Chaparro-Huerta V, Flores-Soto ME, Merin Sigala ME, Barrera de Leon JC, Lemus-Varela ML, Torres-Mendoza BM, et al. Proinflammatory Cytokines, Enolase and S-100 as Early Biochemical Indicators of Hypoxic-Ischemic Encephalopathy Following Perinatal Asphyxia in Newborns. Pediatr Neonatol. 2017; 58(1):70–6. Cytokines have been shown to be useful biomarkers after hypoxic-ischemic insults in transgenic mice. S-100 and enolase are promising candidate biomarkers for HI because they have been correlated with tissue damage in different experimental models. [PubMed: 27522459]

20. Celik Y, Atici A, Gulasi S, Makharoblidze K, Eskandari G, Sungur MA, et al. The effects of selective head cooling versus whole-body cooling on some neural and inflammatory biomarkers: a randomized controlled pilot study. Ital J Pediatr. 2015; 41:79. [PubMed: 26472263]

21*. Li Y, Dammer EB, Zhang-Brotzge X, Chen S, Duong DM, Seyfried NT, et al. Osteopontin Is a Blood Biomarker for Microglial Activation and Brain Injury in Experimental Hypoxic-Ischemic

Encephalopathy. eNeuro. 2017; 4(1) Plasma osteopontin levels at 48 hours post-HI parallel the severity of brain damage at 7 days recovery which suggests that osteopontin may be a prognostic blood biomarker for HIE.

22*. Fiala M, Baumert M, Surmiak P, Walencka Z, Sodowska P. Umbilical markers of perinatal hypoxia. Ginekol Pol. 2016; 87(3):200–4. Asphyxiated neonates demonstrate elevated NGAL and activin A levels. The correlation of NGAL with clinical and biochemical signs of neonatal hypoxia has led these investigators to believe that NGAL could be a better marker of perinatal hypoxia than activin A. [PubMed: 27306129]

23*. Wechselberger K, Schmid A, Posod A, Hock M, Neubauer V, Fischer-Colbrie R, et al. Secretoneurin Serum Levels in Healthy Term Neonates and Neonates with Hypoxic-Ischaemic Encephalopathy. Neonatology. 2016; 110(1):14–20. Secretoneurin levels are elevated in cord blood in neonates suffering from HIE suggesting it may be useful as a biomarker for this condition. [PubMed: 26968040]

24*. Toorell H, Zetterberg H, Blennow K, Savman K, Hagberg H. Increase of neuronal injury markers Tau and neurofilament light proteins in umbilical blood after intrapartum asphyxia. J Matern Fetal Neonatal Med. 2017:1–5. The levels of both Tau and neurofilament increase significantly after asphyxia and correlate with the severity of the insult.

25. Douglas-Escobar M, Yang C, Bennett J, Shuster J, Theriaque D, Leibovici A, et al. A pilot study of novel biomarkers in neonates with hypoxic-ischemic encephalopathy. Pediatr Res. 2010; 68(6): 531–6. [PubMed: 20736881]

26*. Wang KK, Yang Z, Sarkis G, Torres I, Raghavan V. Ubiquitin C-terminal hydrolase-L1 (UCH-L1) as a therapeutic and diagnostic target in neurodegeneration, neurotrauma and neuro-injuries. Expert Opin Ther Targets. 2017; 21(6):627–38. UCH-L1 is emerging as a promising neuron-derived biomarker for traumatic brain injury, ischemic and homographic stroke, pediatric HIE, epileptic seizures and cardiac arrest showing that it has strong potential as a robust and universal biomarker target for various forms of CNS injury. [PubMed: 28434268]

27**. Chafer-Pericas C, Cernada M, Rahkonen L, Stefanovic V, Andersson S, Vento M. Preliminary case control study to establish the correlation between novel peroxidation biomarkers in cord serum and the severity of hypoxic ischemic encephalopathy. Free Radic Biol Med. 2016; 97:244–9. Novel perioxidation biomarkers reflecting oxidative damage were found to be significantly increased in severe postnatal acidemia, and when measured in cord blood may be predictive of neonatal encephalopathy. [PubMed: 27296840]

28. El-Mazary AA, Abdel-Aziz RA, Mahmoud RA, El-Said MA, Mohammed NR. Correlations between maternal and neonatal serum selenium levels in full term neonates with hypoxic ischemic encephalopathy. Ital J Pediatr. 2015; 41:83. [PubMed: 26511525]

29. Espana LY, Lee RM, Ling JM, Jeromin A, Mayer AR, Meier TB. Serial Assessment of Gray Matter Abnormalities after Sport-Related Concussion. J Neurotrauma. 2017

30. Huang W, Besar K, Lecover R, Dulloor P, Sinha J, Martínez Hardigree JF, Pick C, Swavola J, Everett AD, Frechette J, Bevan M, Katz HE. Label-free brain injury biomarker detection based on highly sensitive large area organic thin film transistor with hybrid coupling layer. Chemical Science. 2014; 5(1):416–26.

31. Song J, Dailey J, Hui L, Hyun-June J, Zhang P, Wang J, et al. Biosensor for Label-Free Glial Fibrillary Acidic Protein Detection with Polyethylene Glycol-Containing Bioreceptor Layer. Advanced Functional Materials. 2017; 27(20)

32. Zheng G, Lieber CM. Nanowire biosensors for label-free, real-time, ultrasensitive protein detection. Methods Mol Biol. 2011; 790:223–37. [PubMed: 21948419]

33. Chiang MC, Lien R, Chu SM, Yang PH, Lin JJ, Hsu JF, et al. Serum Lactate, Brain Magnetic Resonance Imaging and Outcome of Neonatal Hypoxic Ischemic Encephalopathy after Therapeutic Hypothermia. Pediatr Neonatol. 2016; 57(1):35–40. [PubMed: 26141483]

34*. Ahearne CE, Chang RY, Walsh BH, Boylan GB, Murray DM. Cord Blood IL-16 Is Associated with 3-Year Neurodevelopmental Outcomes in Perinatal Asphyxia and Hypoxic-Ischaemic Encephalopathy. Dev Neurosci. 2017; 39(1–4):59–65. Interleukin-16 may be an early biomarker of severe injury and aid in the long-term prognostication infants with HIE. [PubMed: 28490023]

35. Ennen CS, Huisman TA, Savage WJ, Northington FJ, Jennings JM, Everett AD, et al. Glial fibrillary acidic protein as a biomarker for neonatal hypoxic-ischemic encephalopathy treated with whole-body cooling. Am J Obstet Gynecol. 2011

36. Chalak LF, Sanchez PJ, Adams-Huet B, Laptook AR, Heyne RJ, Rosenfeld CR. Biomarkers for severity of neonatal hypoxic-ischemic encephalopathy and outcomes in newborns receiving hypothermia therapy. J Pediatr. 2014; 164(3):468–74. e1. [PubMed: 24332821]

37. Looney AM, Ahearne C, Boylan GB, Murray DM. Glial Fibrillary Acidic Protein Is Not an Early Marker of Injury in Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy. Front Neurol. 2015; 6:264. [PubMed: 26733938]

Key Points

1. While new single biomarker studies continue to emerge, utilizing metabolomic profiling to more comprehensively understand the effects of injury and treatment on entire pathways following neonatal brain injury may identify new therapeutic targets in neonatal brain injury.
2. A number of biomarkers used to identify other conditions are now being used to identify neonatal neurologic injury. Markers of cardiac injury are increasingly useful in this respect.
3. Cytokine biomarkers in a relevant pre-clinical model of HIE identify a pro-inflammatory surge during the rewarming period following therapeutic hypothermia. If confirmed these studies may reveal an additional therapeutic target in neonatal HIE.
4. Until recently, very few biomarker studies in neonatal brain injury included post hospital outcomes. Future studies will need to include these data to provide maximal information about their utility.