Review Article

Biomarkers of Birth Asphyxia in Neonates

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Abstract

Birth asphyxia is a common cause of neonatal mortality. Identification of severity of asphyxia is vital for prompt management. Biomarkers can be used for timely diagnosis of asphyxia and also helps in prognosis. Serum, CSF, urine, cord blood & magnetic resonance biomarkers for asphyxia in neonates have been studied. Cytokines like IL-6 in CSF, NSE in CSF, Protein S-100b in serum, urine & cord blood, LDH in serum and saliva, CK in serum and urine, cord BDNF, Urinary UA/Cr ratio, GFAP, Glutamate in CSF, PGE2, AST, ALT, Activin A have been studied with varied diagnostic accuracy and feasibility. Research directed towards newer biomarkers like NPBI, Hypoxanthine, total hydroperoxides, AOPP, UCHL-1 & pNFH-1 for early identification of severe asphyxia have shown promising results. Cardiac biomarkers like Troponin T & I, BNP, CK-MB may aid in longterm outcome. NRBC count still remains as the oldest and best-described biomarker of asphyxia. Use of Proton & Nuclear Magnetic Resonance Spectroscopy on day 1 apart from conventional MRI have opened a new era of MR Biomarkers in neonatal asphyxia. Early identification of severity of asphyxia with judicious use of biomarkers can make a huge difference in the management and outcome of birth asphyxia.

Keywords: Birth asphyxia, Biomarkers, Cytokines in birth asphyxia

Introduction

Birth asphyxia is a common cause of neonatal morbidity and mortality [1, 2]. Similar degrees of insult may completely spare one infant and devastate another, so very sensitive parameters/ Biomarkers are necessary to predict the outcome [3,4,5]. Biomarkers are used to identify injury, its extent , timing and likely outcome [6]. Biomarkers in neonatal HIE can be used to (i) determine the need to intervene with therapeutic hypothermia and (ii) for prognosis. Several biomarkers like Brain-specific CK, LDH, Lactate/ Creatinine ratio, GFAP, Uric acid, Hypoxanthine, Glutamate, NSE, Protein-S, BDNF and S100B in the blood or CSF, Urine Lactate/ Creatinine ratio, first urine S100B have been investigated in infants with asphyxia [6-17]. Recently inflammatory cytokines (TNF-alpha, IL-1-beta, IL-6, IL-8) have been implicated in the biochemical pathways leading to hypoxic-ischemic injury [6,13,14,15,18-27].

Cytokines: Cytokine activation, as manifested by increased IL-1β in the CSF is positively correlated with the severity and outcome of HIE [23,28]. IL-1 seems to be a better predictor of HIE than TNF-alpha [29]. IL-6 is a pleiotropic cytokine produced from both astrocytes and microglial cells within the CNS [30-32]. CSF and serum IL-6 levels significantly correlated with the degree and outcome of encephalopathy [7,17,18,28,33]. A pilot study revealed that IL-6 concentrations were 376-fold higher in noninfected HIE infants compared with healthy newborns [34]. Cutoff value 25.9 pg/mL had good predictive values for long term outcome (PPV: 100%; NPV: 86%; sensitivity: 100%) [7]. CSF IL-6 was higher in HIE stage 3 (range, 65-2250 pg/mL) when compared with neonates with HIE stage 0 to 2 (<2 pg/mL) [35].

Neuron Specific Enolase: NSE is released into both CSF and serum after CNS damage [36-40]. Measurements of NSE are rapid, nonexpensive, simple to perform and widely available [41]. CSF NSE levels significantly correlated with the degree and outcome of asphyxia [7,11-15,17]. Following asphyxia, CSF NSE had high predictive values (PPV: 90%; NPV: 55%; sensitivity:86%; specificity: 64%) for adverse outcome [7]. However Serum NSE had relatively lower values (PPV: 56%; specificity: 67%) for predicting moderate to severe HIE [7,15].

Serum Protein S-100B: S100B protein is a cytosolic calcium-binding protein [9,42]. Because of its molecular weight (21 kDa), S100B may be detected in peripheral blood only if the integrity of the blood–brain barrier is disrupted [41]. Its estimation is rapid, nonexpensive and widely available 41]. Elevated levels are reported after asphyxia [15,38,43-56]. There was a significant difference in S100B levels between moderate or severe HIE and

mild HIE groups [45,57]. Sensitivity and specificity was higher on day 3 (96.7% and 95% respectively) for predicting asphyxia [57]. A combination of serum protein S-100 and CK-BB had a high PPV (83%) and specificity (95%) for predicting moderate to severe HIE [18].

Urinary S100B: S100B may also be detected in urine following asphyxia [41]. Urinary S100B was significantly increased in infants who experienced early neonatal death following asphyxia [58]. Its concentration in the first urine after birth was significantly higher in patients who had HIE than in controls [48]. The level gradually increased and reached the highest level in the third day of life [57]. Urinary S100b concentrations above 1 mcg/L predicted neonatal death with a sensitivity and specificity of 100%, and concentrations were not affected by renal failure [48,59].

Cord Blood S100B: Cord blood concentration of S100B has been linked to HIE [17]. Cord blood S100B > 2.02 mg/L had a sensitivity of 87% and a specificity of 88% for predicting the development of moderate or severe HIE [45].

Serum Lactate Dehydrogenase : Excellent diagnostic ability of serum LDH for asphyxia has been reported in literature [60-65]. Raised Serum LDH level in the first six hours predicted the development of HIE between 6-72 hours after birth [16]. At a cut-off value of 2812 IU/L, it had 90% sensitivity, 96.7% specificity, 96.4% PPV & 91% NPV for diagnosis of HIE [66]. In a retrospective study, serum LDH successfully predicted an abnormal mental or psychomotor development index at 18 months of age in neonates with HIE [67].

Salivary Lactate Dehydrogenase: Salivary LDH may rise in neonates with asphyxia because of either hypoxic–ischaemic damage to the salivary glands or leakage from plasma [68,69]. Measuring salivary LDH provided an early and accurate diagnosis of HIE and could be used as a triage tool [66,70]. Salivary LDH was significantly higher in the HIE group(median 2578) than in the control group (median 558.5,$p < 0.001$)[66]. At a cut-off value of 894 IU/L, it had 90% sensitivity,73.3% specificity, 77.1% PPV & 88% NPV for the diagnosis of HIE [66].

Creatine Kinase : Serum CK is useful as a screening test and was also predictive of long term outcome [16,71]. Level > 2860 IU/L in the first six hours of life predicted the development of HIE between 6-72 hours after birth [16]. Urinary CK-BB levels >42 ng/L was predictive of death following asphyxia with a sensitivity of 90.9%, a specificity of 94.9%, PPV of 83.3% & NPV of 97.4% [58].

Brain-Derived Neurotrophic Factor : Newborns who have HIE have higher cord plasma BDNF levels when compared with healthy neonates [72,73]. BDNF levels at delivery and at 72 hour postnatal were predictors of poor outcome [72].

Urinary Uric Acid / Creatinine Ratio: UA/Cr is a well-defined biomarker in predicting the severity and outcome of HIE [11-15].

Glial Fibrilary Acidic Protein: GFAP is a cytoskeleton intermediate filament protein only released into the blood upon astrocyte death [17]. It has been used as a predictor of mortality or poor neurological outcomes in children [17,74]. Concentrations of > 0.15 ng/mL during the first 2 days in asphyxiated neonates correlate with abnormal outcome [75].

Glutamate : Glutamate has recently been reported as being present in the CSF of asphyxiated newborns and its level has been shown to correlate with the grade of HIE and outcome [76,77].

Prostaglandin E2: Acute hypoxia increases the activity of microsomal prostaglandin E synthase–1 in endothelial cells of the BBB and the subsequent release of PGE2 beyond the BBB [78,79,80]. PGE2 metabolite levels correlated to a low Apgar score at 5 min ($p < 0.01$) and 10 min ($p < 0.01$), a low pH ($p < 0.001$) and HIE score ($p < 0.05$) [81].

AST, ALT: Serum AST and ALT were higher in infants with moderate and severe asphyxia in comparison with those with no asphyxia [82].

Activin A: Activin A also seems to be a reliable marker of perinatal hypoxia [83].

Newer Biomarkers: Indirect markers of increased FR release and oxidative stress during fetal/ neonatal asphyxia have recently emerged, with reports of increased plasma advance oxidative protein products (AOPP) and non-protein-bound iron (NPBI) in plasma and red cells [84-88]. Hypoxanthine, total hydroperoxides and AOPP levels were found to be significantly higher in cord blood and on 7th day blood samples of hypoxic newborns than controls [83]. Serum UCHL-1 (found in neuronal cell bodies), pNFH-1 (found in white matter brain regions) were noted to be predictive of severe HIE [89].

Cardiac Biomarkers: Cardiac biomarkers may aid in longterm neurodevelopmental outcome prediction

following neonatal hypoxic-ischaemia. Biomarkers such as troponin and BNP may aid in outcome prediction [90].

Troponin-T: Newborns with severe HIE have significantly higher serum troponin-T concentrations than other asphyxiated groups (mild to moderate) and healthy neonates on day 1 of life [91,92]. Troponin-T remains significantly higher in the severely asphyxiated group compared with the mild group on days 3 and 7 [82]. Value > 0.1 microgram ⁄ L may predict severity of encephalopathy and mortality [92].

Troponin-I: Cord blood troponin-I levels are significantly higher in infants who sustain a hypoxic insult with or without ensuing encephalopathy compared with normals ($p < 0.0001$) [93-96]. A cut-off value 0.35 microgram ⁄ L may predict severity of neonatal hypoxic ischaemia [93,94]. Cord troponin-I is the marker with highest specificity (86%), sensitivity (88%), NPV (85%), PPV (88%) for prediction of perinatal hypoxia [93]. It is the most sensitive factor for predicting early death [94,96].

CK-MB: Levels of CK-MB began to rise within the first few hours of life and are significantly higher in moderate and severe grades of HIE compared with mild grades and normal controls within the first 2–4 hour [93].

Urinary Biomarkers: Urine lactate/creatinine is difficult to interpret, because lactate is a global marker of anaerobic metabolism and would not be brain-specific [6]. However Urine S100 is brain-specific [6] & is a very promising marker correlating well with tissue injury in HIE [97,98].

Nucleated Red Blood Cell Count: NRBC count is one of the oldest and best-described biomarker of asphyxia [57,99,100]. It was used as an early marker for subsequent neurological impairment in neonatal hypoxia [83,100-103]. Postnatal NRBCs distinguished between mild and moderate/ severe encephalopathy in normothermic infants but not in infants undergoing therapeutic hypothermia [57,104,105,106]. The increase in NRBCs associated with hypoxia is secondary to raised IL-6 and erythropoietin (EPO) [104,107,108]. The sensitivity and specificity were highest at the first day (96.6% and 100% respectively)[57].

Magnetic Resonance Biomarkers: Meta-analysis suggests that deep gray matter Lac/NAA and Lac/Cr are the most accurate quantitative MR biomarker for prediction of neurodevelopmental outcome after HIE. Thalamic or basal-ganglia lactate/total creatine had sensitivity of 77% and 94% specificity for predicting severe asphyxia [109]. Lactate/choline, NAA/choline, NAA/creatine had sensitivities and specificities of 84% and 81% ; 59% and 72% ; and 61% and 71% respectively [109].

Proton Magnetic Resonance Spectroscopy: During the first 96 h of life H-MRS could be a useful early prognostic tool in predicting the outcome of asphyxiated neonates. Myo-inositol/ N-Acetyl-Aspartate ratio was found to be the best and time-independent predictor with 85.71% sensitivity and 91.30% specificity [110]. Deep gray matter lactate/N-acetyl aspartate (Lac/NAA) peak-area ratio had 82% sensitivity and 95% specificity for predicting severe asphyxia [110]. Lac/NAA had better diagnostic accuracy than conventional MRI performed at any time during neonatal period. When the MR biomarker was determined at any time in the age range 1 to 30 days, Lac/NAA had a significantly higher specificity than conventional MRI 98% vs 76% [109]. Lac/NAA sensitivity of 86% was comparable to that for conventional MRI of 80% [109].

Nuclear Magnetic Resonance Spectroscopy : When the metabolite profile of Umbilibal Cord Blood was analysed using NMR spectroscopy, a characteristic pattern of raised glycerol + succinate reflecting critical energy failure occurred in those infants with severe encephalopathy and very low voltage EEG ($p < 0.001$) [110].

Conclusion

A therapeutic window exists in the early hours following asphyxia, when intervention can attenuate activation of the neurotoxic cascade that leads to ultimate cell death [111]. Early identification of severity of asphyxia with the use of biomarkers can make a huge difference in the management and outcome of birth asphyxia.

Abbreviation

ALT	Alanine Transaminase
AOPP	Adance Oxidation Protein Products
AST	Aspartate Transaminase
BBB	Blood Brain Barrier
BDNF	Brain Derived Neurotrophic Factor
BNP	Brain Natriuretic Protein
CK	Creatine Kinase
CNS	Central Nervous System
CSF	Cerebro Spinal Fluid
EPO	Erythropoietin
FR	Free Radical
GFAP	Glial Fibrilary Acidic Protein
HIE	Hypoxic Ischemic Encephalopathy
IL	Interleukin

IU/L International units/litre
kDa kiloDalton
Lac/Cr Lactate/Creatinine
Lac/NAA Lactate/N-acetyl aspartate
LDH Lactate Dehydrogenase
MRS Magnetic Resonance Spectroscopy
NAA N-Acetyl Aspartate
ng/L nanogram/litre
ng/mL nanogram/millilitre
NPBI non-protein-bound iron
NPV Negative Predictive Value
NRBC NUcleated Red Blood Cell
NSE Neuron Specific Enolase
PGE2 prostaglandin E2
PPV POsitive Predictive Value
TNF Tumour Necrosis Factor
UA/Cr Uric acid/Creatinine

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