

Table 2: Summary of metabolomic studies in human neonates with perinatal asphyxia-hypoxic-ischemic encephalopathy (HIE).

Author/year	Experimental model	Aim	Biological fluid	Analytical platform	Key findings
Chu et al/2006 ⁵⁶	Asphyxiated neonates	Study the metabolomic profile in urines of neonates with severe asphyxia and subsequent neurodevelopmental handicap	Urine	High throughput MS	<ul style="list-style-type: none"> ● Increased ethylmalonate, 3-hydroxy-3-methylglutarate, 2-hydroxy-glutarate and 2-oxo-glutarate were associated with good neonatal outcome ● Increased glutarate, methylmalonate, 3-hydroxy-butyrate and orotate were associated with poor outcome
Walsh et al/2012 ⁴²	Newborns with HIE	Investigate the metabolomic profile	Umbilical cord blood	LC-MS/MS	<ul style="list-style-type: none"> ● 29 metabolites showed alterations from 3 distinct classes (amino acids, acylcarnitines and glycerophospholipids) ● 9 metabolites were significantly altered in HIE ● A model of 5 metabolites clearly delineated severity of asphyxia and classified HIE infants ● Disruption to energy, nitrogen and lipid metabolism was evident in both asphyxia and HIE
Reinke et al/2013 ²⁴	Asphyxiated neonates	Investigate pathophysiology of HIE	Umbilical cord blood	¹ H NMR	<ul style="list-style-type: none"> ● 37 metabolites were significantly altered between the study groups ● Acetone, 3-hydroxybutyrate, succinate, and glycerol were significantly differentially altered in severe HIE ● A model using 3-hydroxybutyrate, glycerol, O-phosphocholine and succinate predicted HIE severity
Longini et al/2015 ²¹	Asphyxiated neonates	Evaluate the effects of asphyxia on newborn metabolites	Urine	¹ H NMR	<ul style="list-style-type: none"> ● Lactate, glucose, trimethylamine N-oxide, threonine and 3-hydroxyisovalerate were the metabolites more characterizing the asphyxiated neonates ● After 24-48 hours from resuscitation, asphyxiated neonates showed a recovery pattern but still could be differentiated from controls

Noto et al/2016 ⁵⁷	Asphyxiated neonates	Identify the metabolome in perinatal asphyxia and to follow changes over time	Urine	GC-MS	<ul style="list-style-type: none"> ● The metabolomic profile of neonates who died after day 7 of life was significantly different from that of survivors
Ahearne et al/2016 ⁵⁸	Infants with perinatal asphyxia and HIE	Investigate if alterations of succinate, glycerol, 3-hydroxybutyrate and O-phosphocholine can predict 3-year neurodevelopmental outcome	Umbilical cord blood	¹ H NMR	<ul style="list-style-type: none"> ● The metabolite index significantly correlated with outcome, predicting severe outcome and intact survival ● There was no correlation between the index score and performance in the individual Bayley-III subscales (cognitive, language, motor) ● The metabolite index was not superior to EEG or the Sarnat score
Deniham et al/2017 ⁴³	Asphyxiated neonates (recovering and developing HIE)	Examine early metabolic alterations in infants recovering perinatal asphyxia vs. those who developed HIE	Umbilical cord blood	FT-ICR mass spectrometry	<ul style="list-style-type: none"> ● Perturbed metabolic pathways and potential biomarkers specific to perinatal asphyxia and HIE were identified, which if measured at birth, may help direct treatment
Sanchez-Illana et al / 2017 ⁵⁰	Newborns with HIE	Determination of lipid peroxidation biomarkers in newborn plasma samples	Plasma	LC-MS	<ul style="list-style-type: none"> ● Isoprostanooids provide predictive power of oxidative stress related pathologies
Sarafidis et al/2017 ²⁶	Asphyxiated term neonates with HIE	Identify metabolic changes in neonates with HIE	Urine	LC-MS/MS	<ul style="list-style-type: none"> ● Asphyxiated neonates were clearly separated from controls ● Discriminant metabolites involved pyruvic acid, amino acids, acylcarnitines, inositol, kynurenine, hippuric acid and vitamins

MS: mass spectrometry, LC-MS: Liquid Chromatography - Mass Spectrometry, NMR: nuclear magnetic resonance (spectroscopy), HIE: hypoxic-ischemic encephalopathy, GC-MS: gas chromatography mass spectrometry, FT-ICR: Fourier-transform ion cyclotron resonance.