

subjects (neuromotor score, NMS  $\geq 2$ , or Bayley Scales of Infant Development II or III MDI  $< 70$  or cognitive score  $< 85$ ).

Chorioamnionitis (42 subjects) was associated with a lower risk of moderate-severe brain injury (OR 0.3; 95%CI 0.1–0.7;  $p=0.003$ ), and trended toward lower risk of adverse neurodevelopment. Infant infection (32 subjects) trended toward association with moderate-severe injury (OR 1.6; 95%CI 0.8–3.5;  $p=0.2$ ), and was significantly associated with an abnormal NMS (OR 3.4; 95%CI 1.2–10.2;  $p=0.03$ ) but not cognitive outcome. After adjusting for hypothermia and severity of encephalopathy, maternal infection remained associated with a lower risk of brain injury, whereas the association between infant infection and NMS was no longer significant.

These preliminary results are in keeping with animal studies that suggest that the timing of an inflammatory signal may determine whether infection is injurious or protective.

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# GENES IMPORTANT IN INFLAMMATION, APOPTOSIS, TRANSCRIPTION REGULATION AND ANGIOGENESIS ARE INDUCED IN THE NEWBORN MOUSE BRAIN AFTER HYPOXIA-REOXYGENATION (HR)

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**Background and Aims** Pathogenesis of birth asphyxia has yet to be fully elucidated. To explore the mechanism of HR injury we followed the temporal profile of *a priori* selected genes in the newborn mouse brain.

**Methods** 84 C57BL/6 mice (postnatal day 7) were randomized to 120 minutes of hypoxia (FiO<sub>2</sub> 0.08, n=64) or 180 minutes in air (controls (C21), n=20). The hypoxia group was randomized to 30 min reoxygenation with FiO<sub>2</sub> 0.60 (H60) or air (H<sub>2</sub>1). After observation in air for 0, 150, 300 minutes or 3 days, organs were harvested. Homogenate of hippocampus and striatum was analyzed for mRNA expression of 44 genes by real-time PCR.

**Results** *Lcn2*, *Mt14*, *Hmox1* and *Vegfa* were significantly up-regulated ( $p<0.05$ ) after 0–300 min observation when comparing H<sub>2</sub>1vsC21 and H60vsC21. *Ccl2*, *Ccl12* and *Tnf* were up-regulated from 0–150 min, *Stat3* from 150–300 min, while *Cnd1* was down-regulated at 0 min in both comparisons. In the H<sub>2</sub>1vsC21 comparison at 0 min, *Neil3* and *Apa1* were down-regulated. When comparing H60vsH21, *Cxcl10* (0 min) and *Hmox1* (300 min) were up-regulated while *Neil3* (0 min) was down-regulated. There were no significant gene expression changes after 3 days.

**Conclusions** Genes important in inflammation (*Lcn2*, *Mt14*, *Ccl2*, *Ccl12*, *Cxcl10*, *Tnf*, *Hmox1*), apoptosis (*Lcn2*, *Mt14*, *Tnf*, *Hmox1*, *Vegfa*), angiogenesis (*Vegfa*), and transcription regulation (*Stat3*) were induced up to 300 minutes after hypoxia-reoxygenation while the DNA-glycosylase *Neil3* was suppressed. The up-regulation of the pro-inflammatory cytokine *Cxcl10* after hyperoxic compared to normoxic reoxygenation, confirms that hyperoxia induces additional inflammation.

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# PROGNOSTIC TESTS IN TERM NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY: A SYSTEMATIC REVIEW

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**Background and Aims** Hypoxic Ischemic Encephalopathy (HIE) following perinatal asphyxia in term neonates is associated with long term neurological sequelae or demise. The aim of this systematic review was to investigate the prognostic value of currently used clinical tests in neonatal patients with HIE.

**Methods** MEDLINE, EMBASE, Central and CINAHL were searched until November 2011. Studies were included if they: (1) concerned infants with a gestational age  $\geq 36$  weeks suffering perinatal asphyxia and HIE; (2) evaluated prognostic tests in either cooled or non-cooled patients; (3) reported on neurodevelopmental outcome results at a follow up age  $\geq 18$  months. Study selection, assessment of methodological quality, and data extraction was performed by three independent reviewers. Pooled sensitivities and specificities of investigated tests were calculated when possible.

**Results** Included in the analysis were 29 studies describing 13 different prognostic tests conducted 1631 times in 1306 term neonates. Investigated tests comprised a range of imaging modalities, neurophysiological tests and clinical neurological exams. Most promising neurophysiology tests (first week of life) were: aEEG (sens. 0.93, [95%CI 0.78–0.98]; spec. 0.90 [0.60–0.98]); EEG (sens. 0.92 [0.66–0.99]; spec. 0.83 [0.64–0.93]) and VEP (sens. 0.90 [0.74–0.97]; spec. 0.92 [0.68–0.98]).

**Conclusions** The available evidence suggests an important role for aEEG, EEG, and VEP. Given the heterogeneity of the tests' performance and outcomes studied, accurate predictions of long term outcomes in these critically ill neonates await the results of well designed large prospective studies that evaluate the best possible combination and timing of diagnostic tests.

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# THE IMPACT OF HYPOTHERMIA ON POST-NATAL BLOOD BIOMARKERS OF NEONATAL HYPOXIC ISCHAEMIC ENCEPHALOPATHY

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Numerous post-natal biomarkers of hypoxic ischaemic encephalopathy (HIE) severity have been proposed before the era of hypothermia. It is unclear if hypothermia impacts upon these potential biomarkers, and therefore whether previous findings are now valid. The aim of this study was to determine if hypothermia alters the discriminative ability of post-natal nucleated red blood cells (NRBCs) to distinguish between mild and moderate/severely encephalopathic infants.

**Methods** A prospective cohort study recruited term infants with HIE. The grade of HIE was categorised using Sarnat score, and multi-channel EEG. The recruitment period (2003–2012), spanned the introduction of hypothermia. Therefore the discriminative ability of the NRBC count for grade of encephalopathy could be compared in moderate/severely encephalopathic infants who did and did not receive hypothermia.

**Results** 86 infants with HIE were included in the study, 40 were mild, 26 moderate (14 normothermic, 12 hypothermic), and 18 severe (10 normothermic, 8 hypothermic). In the normothermic group, the NRBC count discriminated between mild and moderate/severe Sarnat scores ( $p=0.016$ ), but not in the hypothermic group ( $p=0.297$ ). This change was due to a decrease in NRBCs among infants with a moderate Sarnat score receiving hypothermia. This occurred despite these infants having a significantly worse 5 minute Apgar score ( $p<0.001$ ) and background EEG at 6 hours ( $p=0.032$ ) than their normothermic counterparts.

**Conclusion** This study has demonstrated that hypothermia can impact upon early post-natal blood biomarkers of HIE. We therefore advise caution in the use of these samples when studying novel diagnostic biomarkers for HIE in the hypothermic era.