Title

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Abstract

Background—Perinatal infection may potentiate brain injury among children born *preterm*. The objective of this study was to examine whether maternal and/or neonatal infection are associated with adverse outcomes among *term* neonates with encephalopathy.

Methods—Cohort study of 258 term newborns with encephalopathy whose clinical records were examined for signs of maternal infection (chorioamnionitis) and infant infection (sepsis). Multivariate regression was used to assess associations between infection, pattern and severity of injury on neonatal MRI, as well as neurodevelopment at 30 months (neuromotor exam, or Bayley Scales of Infant Development II MDI <70 or Bayley III cognitive score <85).

Results—Chorioamnionitis was associated with lower risk of moderate-severe brain injury (adjusted OR 0.3; 95% CI 0.1–0.7, P=0.004), and adverse cognitive outcome in children when compared to no chorioamnionitis. Children with signs of neonatal sepsis were more likely to exhibit watershed predominant injury than those without (P=0.007).

Conclusions—Among neonates with encephalopathy, chorioamnionitis was associated with a lower risk of brain injury and adverse outcomes, whereas signs of neonatal sepsis carried an elevated risk. The etiology of encephalopathy and timing of infection and its associated inflammatory response may influence whether infection potentiates or mitigates injury in term newborns.

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Conflicts of Interest
None

Introduction

Neonatal encephalopathy, presumed due to hypoxia-ischemia, occurs in 1–3 per 1,000 term births (1,2) and is a major cause of mortality and neurologic disability. Risk factors for adverse outcome include severity of the initial insult (3), abnormal electroencephalogram or severity of clinical encephalopathy and seizures (4,5), as well as pattern and severity of injury on magnetic resonance imaging (MRI) (6,7). Modifiable risk factors include hyperthermia and hypoglycemia (8,9).

Perinatal infection is an additional, potentially modifiable, risk factor for encephalopathy that has been linked to adverse outcomes. Among preterm neonates, chorioamnionitis and neonatal sepsis are associated with brain injury (and specifically white matter injury) and cerebral palsy (2,10–15). However, the role of perinatal infection among *term* neonates, especially those with a history of encephalopathy, is not well understood. Past studies suggest that chorioamnionitis is not an added risk factor for brain injury, whereas others studies suggest that neonatal sepsis may lead to impaired oxidative metabolism and abnormal neurodevelopmental outcomes in childhood (16,17). Definitive conclusions, however, are limited by the small sample sizes of these studies and/or lack of long-term outcomes.

In this study. we examined the hypothesis that, among term newborns with encephalopathy, maternal chorioamnionitis and/or signs of neonatal sepsis are associated with a higher risk of neonatal brain injury, and worse long-term neurodevelopmental outcome.

Materials and Methods

Subjects

Neonates were enrolled in an ongoing prospective cohort study of the use of MRI to predict outcome following risk of hypoxic-ischemic brain injury and encephalopathy from the Intensive Care Nursery of the University of California, San Francisco (UCSF). Inclusion criteria for the cohort are gestational age   36 weeks and any one of the following criteria: (1) first blood gas or umbilical cord artery pH < 7.1, (2) first blood gas or umbilical cord artery base deficit >10, and/or (3) a 5-minute Apgar score   5. These broad inclusion criteria were chosen to encompass newborns with a wide range of injury and neurodevelopmental outcome and have been used in previous publications by our group (18). Neonates with congenital malformation, inborn error of metabolism, or congenital infection that was suspected or diagnosed based on clinical, laboratory, or radiographic data were excluded. The UCSF Committee on Human Research approved the research protocol.

From December 1993 to September 2011, 295 neonates were enrolled, and imaged in the newborn period according to protocol. Trained neonatal research nurses prospectively collected prenatal, perinatal, and postnatal variables from maternal and neonatal hospital records. A pediatric neurologist determined encephalopathy scores (19). Therapeutic hypothermia using 72 hours of whole body cooling was initiated at our institution in November 2007 (20). Patients with seizures were managed at the discretion of the treating physician, typically with phenobarbital as the first-line agent.

For the current study, the obstetric charts, neonatal charts, and microbiology reports were reviewed for signs of maternal and postnatal infection. *Clinical chorioamnionitis* was defined as maternal temperature >37.8 °C and uterine tenderness, or as maternal fever <u>or</u> uterine tenderness <u>and</u> one of: (1) maternal tachycardia (>120 beats per minute (bpm), fetal tachycardia (>160 bpm), purulent or foul-smelling amniotic fluid or vaginal discharge, or maternal leukocytosis (total blood leukocyte count >15,000 cells/mm^3) within 72 hours of delivery (21). Presence of *histological chorioamnionitis* was determined by review of the clinical histopathological reports when available (N=37). The treating physician managed chorioamnionitis according to local guidelines. Subjects with clinical and histological evidence of infection were combined for analysis.

Infants were considered to have "signs of neonatal sepsis" if there was a documented bloodstream infection (i.e., blood cultures positive for pathogenic species other than *staphylococcus* epidermis) (22) or if they met the following clinical criteria for suspected sepsis: (1) a low white blood cell count (5,000 cells/mm^3), (2) a low absolute neutrophil count (<2,000 cells/mm^3), or (3) a high immature/total ratio (0.45) <u>and</u> a neonatal temperature >38.0°C (23,24) within the first 7 days of life.

Magnetic Resonance Imaging—MRI was performed in all newborns at a median of 5 days of life (interquartile range 4, 7 days). A specialized neonatal circularly polarized head coil was used on a 1.5-Tesla Signa EchoSpeed system (GE Medical Systems, Fairfield, CT). Pentobarbital was used as sedation, if necessary. Imaging sequences were optimized for the neonatal brain and included: (1) Sagittally acquired volumetric fast IR-prepped spoiled gradient echo images using 1mm partition size, 256×256 acquisition matrix, 1 NEX and 18 cm FOV, (2) T2-weighted axial dual echo, SE with TR/TE of 3000/60,120 ms, 4 mm thickness, 1 excitation and 192 × 256 acquisition matrix, (3) diffusion weighted imaging (DWI) for subjects enrolled from 1998 onward, SE echoplanar imaging diffusion sequence with TR/TE 7000/99 ms, field of view 180 mm, 3-mm thickness (no skip), 128 × 128 acquisition matrix, b value of 700 s/m^2 during acquisition in three directions from 1998 to 2003, six directions from 2003–2008, or 30 directions after 2008.

A pediatric neuroradiologist who was blinded to the neonatal course scored T1, T2, and diffusion-weighted images prospectively. Injury to the basal ganglia and thalamus (basal ganglia/thalamus) and the watershed areas were scored independently, using a classification system that is predictive of neurodevelopmental outcome after neonatal encephalopathy[18]. Pattern of injury was defined as "basal ganglia-predominant" (basal ganglia/thalamus scores watershed scores, or maximum basal ganglia/thalamus and watershed scores), "watershed-predominant" (watershed scores > basal ganglia/thalamus scores) or "normal" (basal ganglia/thalamus and watershed scores normal)[6]. Injury was considered "moderate-severe" if the basal ganglia/thalamus score was 2 or watershed score was 3) (25). "Total injury" was considered present if maximal basal ganglia/thalamus *and* watershed scores were present.

Neurodevelopmental Outcome—A developmental psychologist who was blinded to the neonatal course assessed cognitive outcome at a goal age of 30 months. Bayley Scales of Neonatal Development, 2nd edition (BSID-II) were administered prior to June 2008, after

which the Bayley Scales of Neonatal Development, 3rd edition were administered (Bayley-III). For purposes of analysis, a BSID-II mental development index (MDI) <70 or Bayley-III cognitive subscore <85 were considered abnormal (26–28). Neuromotor function was evaluated using the neuromotor score, which is based on tone, reflexes, and power and where 0 is normal and 5 is spastic quadriparesis (29). Neuromotor score ≥ 2 indicates an abnormal neurological examination. BSID II Psychomotor Development Index scores were not available.

Analysis—Statistical analysis was performed using Stata 11 (StataCorp LP, College Station, Texas). Neonates with or without either maternal or infant infection were independently examined in association with clinical and outcome variables using χ^2 and Fisher's exact test for categorical variables, Kruskal-Wallis equality-of-populations rank test for non-parametric continuous variables, and ANOVA for normally distributed continuous variables. There was no interaction between maternal chorioamnionitis and signs of neonatal sepsis, and as such, the two predictors were analyzed separately as *affected group* compared with *unaffected group*. Logistic regression was used to examine the association between the infection and presence of severe brain injury, neuromotor score ≥ 2, or abnormal cognitive outcome. To build a multivariable model, we used backward stepwise regression starting with all variables associated with either of the predictors, and at least one outcome at P<0.2, as well as first pH as a face value variable.

Results

Of the 295 patients enrolled into the cohort during the study period, 37 were excluded for insufficient documentation to assess either maternal or neonatal infection (35 subjects), or MR images that were motion degraded (2 subjects). The clinical characteristics of the 258 subjects included in this analysis are presented in Table 1.

Forty-two (16%) of neonates had a maternal history of chorioamnionitis (28 with clinical chorioamnionitis, 20 with histological chorioamnionitis, 6 with both clinical and histological), whereas 29 (11%) had proven or suspected sepsis (4 with confirmed bloodstream infection and 25 with suspected sepsis). Six subjects (2%) had both maternal chorioamnionitis and signs of neonatal sepsis. Organisms identified from blood cultures included: *Escherichia coli*, 2 subjects, and Group B *streptococci* or unspeciated gram-positive rods, 1 subject each. None of the 55 neonates with cerebrospinal fluid analysis had meningitis. Neonates with maternal chorioamnionitis had less severe markers of perinatal asphyxia; specifically, they had higher pH and higher base excess from the cord gas or initial blood draw, as well as a lower maximal encephalopathy score.

Brain injury

Pattern of injury—Brain injury was present in 61% of subjects. The watershed predominant pattern of injury was the most common pattern, seen in 98 (38%) newborns, whereas 59 (23%) had the basal ganglia/thalamus predominant pattern; the remainder had normal brain imaging.

Infection status was associated with pattern of brain injury (Figures 1 and 2). Whether examining data by the three or the four category classification system, children of mothers with chorioamnionitis were more likely to have normal imaging than those without maternal chorioamnionitis. And the 29 infants with signs of neonatal sepsis were more likely to have injury in the watershed pattern than those without signs of neonatal sepsis. However, among the 4 children with confirmed bloodstream infection, 2 had the basal ganglia/thalamus pattern (group B *strep* and gram positive rods), 1 had the watershed-predominant pattern of injury (*E. Coli*), and 1 had a normal MRI (*E. Coli*).

Severity of injury—Moderate-severe brain injury was present in 45% of subjects. Whereas neonates with maternal chorioamnionitis were less likely to have moderate-severe brain injury as compared to those without maternal chorioaminionitis (OR 0.5; 95% CI 0.1– 0.7, P=0.003, Table 2), neonates with signs of sepsis did not have altered risk of moderate-severe brain injury as compared to those without (OR 1.3, 95% CI 0.8–4.0, P=0.1). Three of the 4 (75%) neonates with confirmed bloodstream infection had moderate-severe brain injury.

The decreased risk of severe brain injury on MRI in neonates with maternal chorioamnionitis remained significant after adjusting for maximal encephalopathy score and first pH (Table 2).

Neurodevelopmental outcome

Sixteen newborns died prior to the 30-month evaluation (6%). Neither maternal chorioamnionitis nor signs of neonatal sepsis in the neonate was associated with a higher risk of death (5% with maternal chorioamnionitis died vs 6% without, P=1.0; 10% with signs of neonatal sepsis died vs 6% without, P=0.4).

At the time of analysis, 194 subjects were eligible for 30-month evaluation; 126 had a motor evaluation and 117 had a cognitive evaluation using either BSID II (75 subjects) or Bayley III (42 subjects) at a median age of 31 months (inter-quartile range 30, 32 months). Both cognitive and motor testing was complete in 115 subjects. There were no significant differences in sex, delivery route, birth weight, gestational age at birth, Apgar scores, encephalopathy score, neonatal seizures on EEG, or presence of maternal chorioamnionitis or signs of neonatal sepsis between the children with and without follow-up, and between those tested with BSID II *versus* Bayley III.

Motor outcome—The median neuromotor score was 0 (range 0–5) and 26% had a neuromotor score   2. There was a trend toward lower (more normal) neuromotor score for children with maternal chorioamnionitis when compared with those without (P=0.1). The odds of neuromotor score   2 among those neonates exposed to maternal chorioamnionitis as compared with those without (OR 0.3 95% CI 0.1 – 1.3, P=0.1). In contrast, the median neuromotor score was higher for children with signs of neonatal sepsis (median neuromotor score 2, range 0–5), as compared with those without (median neuromotor score 0, range 0–5, P=0.02). The odds of neuromotor score   2 in children with signs of neonatal sepsis were 4.6 (95% CI 1.5 – 14.6, P=0.009)(Table 3).

After adjusting for maximal encephalopathy score and pH, associations between maternal chorioamnionitis or neonatal signs of neonatal sepsis and risk of neuromotor score 2 were similar, but no longer significant (chorioamnionitis OR 0.5, 95% CI 0.1–1.8, P=0.2 and signs of neonatal sepsis OR 3.4, 95% CI 0.8–13.9, P=0.07).

Cognitive outcome—Seventy-five children were tested using the BSID-II with a median (range) MDI of 86 (range 50, 121). After 2008, cognitive outcome was assessed with Bayley III in 42 children.

Median cognitive composite score was 100 (range 65,145). Considering both scores, 21 (18%) of the assessed children had an abnormal cognitive outcome (23% had an MDI<70 and 10% had a Bayley III cognitive score <85).

Maternal chorioamnionitis was associated with a lower risk of abnormal cognitive testing (none of those with exposure to maternal chorioamnionitis vs 21% of those without had an abnormal score, P=0.03; considering BSID II only, none of those with vs 27% of those without had an abnormal score, P=0.06). Signs of neonatal sepsis were associated with a higher risk of abnormal cognitive score, though the difference was not significant (33% of those with signs of neonatal sepsis vs 16% of those without, OR 1.8, 95% CI 0.8–4.0, P=0.1). Among those children tested with BSID II only, there was no difference (27% of those with vs 22% of those without, OR 1.2, 95% CI 0.4–3.6, P=0.7).

Discussion

In this cohort of term neonatal encephalopathy, children who were exposed to maternal chorioamnionitis had a lower risk of brain injury and adverse outcomes as compared with those without such exposure, whereas children with signs of neonatal sepsis had a higher risk of brain injury and adverse outcomes when compared with those without sepsis. These findings comport with prior animal and human studies that show a variable response of the developing brain to inflammation depending on the timing of exposure and developmental age of the subject (30,31).

There are several possible explanations for the apparent "protective" effect of chorioamnionitis in this cohort. First, it is possible that chorioamnionitis is a less harmful cause of low 5-minute Apgar score and/or cord blood acidosis (which were cohort inclusion criteria) than hypoxia-ischemia, and thus exposed neonates are relatively less affected than other subjects in the cohort. This explanation is supported by the fact that subjects with a maternal history of chorioamnionitis had less severe markers of perinatal asphyxia, though this difference may also come from a wide range of other causes, including obstetric practice differences in response to an infected mother. An alternative explanation for the better outcomes among neonates exposed to chorioamnionitis is that the prenatal timing may have had a preconditioning effect that protected the child against injury from hypoxia-ischemia (30). Past studies provide inconclusive evidence as to the relationship between chorioamnionitis and outcome. Chorioamnionitis has been linked to white matter injury and cerebral palsy in pre-clinical and human studies, with data coming from both individual studies and meta-analyses, and results being strongest among those children born preterm

(32–38). The exact pathophysiology, however, remains inconclusive. Chau *et al* looked carefully at this question by examining a cohort of preterm neonates, and found that histopathological chorioamnionitis was *not* associated with an increased risk of white matter injury (the predominant injury in preterm neonates), nor did it significantly affect measures of brain metabolic and microstructural development, whereas neonatal sepsis and hypotension were associated with these measures, making the neonatal illness that may follow maternal infection a more likely direct cause of adverse outcome (39). The lack of direct association between chorioamnionitis and adverse outcome has also been substantiated among term neonates: an investigation that accounted for severity of neonatal illness (hypotension, need for intubation, neonatal seizures, and encephalopathy) failed to demonstrate a significant relationship between maternal infection and adverse outcome (16). More recently, Harteman *et al* examined the relationship between placental pathology and brain imaging in a cohort of 95 neonates with encephalopathy. The authors found high rates of placental abnormalities among neonates with encephalopathy. As in our study, among subjects with exposure to chorioamnionitis (and especially high grade chorioamnionitis), imaging was more likely to be normal (45% as compared to 27% of those who were not exposed to chorioamnionitis). The authors also found that the watershed predominant pattern was the most common injury. Harteman *et al* report more subjects with basal ganglia injury than we found in our cohort; however, their MR scoring system differs from ours, making exact comparisons difficult (40).

Animal data from Eklind *et al* suggest an explanation for a protective effect of chorioamnionitis leading to an inflammatory environment for the fetus. This group showed that lipopolysaccharide (LPS) enhanced HI injury when administered either 72 hours before or 6 hours after the insult, but *reduced* brain injury when administered 24 hours before the HI injury. The investigators concluded that LPS augmented vulnerability with either acute or chronic administration, but that intermediate interval administration had a protective effect (30). The early sensitizing effect of LPS may be explained by an inflammatory and apoptotic response that is marked by up-regulation of chemokines and cytokines, as well as up-regulation of pro-apoptotic genes (30). However, LPS and other inflammatory mediators have also been shown to have a preconditioning effect similar to that of hypoxia-ischemia. The protective effect may be due to the induction of hypoxia-inducible factor and nitric oxide, as well as inhibition of caspases and induction of the anti-apoptotic system. These factors are important for preconditioning in the setting of hypoxia-ischemia (reviewed in (41)).

The association between neonatal sepsis and adverse outcome is in keeping with animal studies, which demonstrate that exposure to inflammation after the insult potentiates hypoxic-ischemic injury (30). The finding that the watershed pattern of injury was more common in those with neonatal inflammation is similar to what is seen in preterm neonates, who have higher rates of white matter injury following sepsis and necrotizing enterocolitis (13,39,42,43). In the preterm population, this pattern of injury has been attributed to the selective vulnerability of oligodendrocyte precursor cells, and also to blood pressure instability and perturbed cerebral autoregulation, which lead to shifts in cerebral perfusion and oxygenation (44). Blood pressure and cerebral perfusion monitoring data were not

available for this cohort, so we cannot exclude that the association between signs of neonatal sepsis and outcome in this cohort is due to cardiovascular instability and cerebral hypoperfusion.

We acknowledge several limitations of this study. First, it is difficult to precisely measure effects of chorioamnionitis and neonatal sepsis since both conditions exhibit wide variability in presentation and severity. Differences in the quality and detail of the clinical reports, especially from children born in the beginning of the cohort, made it difficult to assess for the presence of clinical maternal infection. Only 37 patients had placental pathological examination, and we were unable to grade the severity of histological chorioamnionitis from the reports. The rate of chorioamnionitis in a similar cohort was higher (46%) (40), suggesting that we may have failed to capture the full burden of maternal infection, a misclassification that would bias us to the null hypothesis, making it more difficult to find associations within our data. Second, despite the large size of the total cohort, we had small numbers of the predictors and outcomes of interest, which may explain why some associations were not significant. The rate of sepsis in our cohort (11%) was very similar to the 5–14% rate seen in the hypothermia trials (45). Third, part of the cohort was lost to follow-up prior to 30 months. Although the neonatal features of those children with and without follow-up are similar, we cannot exclude bias. Fourth, as did many other centers, we switched from the BSID-II to the Bayley-III mid-way through the cohort. When examining the effect of infection on cognitive outcomes, we chose the MDI of the BSID-II with cutoff of 70, and the Bayley-III with cutoff of 85 for a dichotomous outcome measure to account for differences in the scales (26–28). The impact of the change in test is not known: when examining the subgroup of children tested with BSID II, we found no difference in results among those neonates exposed to chorioamnionitis, however, there was no estimated increase in adverse outcome among children with signs of neonatal sepsis. Finally, we also initiated therapeutic hypothermia midway through the cohort. The effect of hypothermia was not significant in this cohort; however, the effect of hypothermia on inflammation in the setting of neonatal encephalopathy is uncertain, and merits further study.

Conclusions

These results suggest that neonatal sepsis potentiate brain injury in term neonatal encephalopathy, whereas chorioamnionitis was not associated with increased injury. Basic and clinical research to elucidate the underlying pathophysiological mechanisms is necessary to better determine the influence of timing of infection in relation to perinatal insult.

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References

1. Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol. 2008; 199:587–95. [PubMed: 19084096]

2. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010; 86:329–38. [PubMed: 20554402]

3. Shah PS, Beyene J, To T, Ohlsson A, Perlman M. Postasphyxial hypoxic-ischemic encephalopathy in neonates: outcome prediction rule within 4 hours of birth. Arch Pediatr Adolesc Med. 2006; 160:729–36. [PubMed: 16818839]

4. Nash KB, Bonifacio SL, Glass HC, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. Neurology. 2011; 76:556–62. [PubMed: 21300971]

5. Spitzmiller RE, Phillips T, Meinzen-Derr J, Hoath SB. Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischemic encephalopathy: a meta-analysis. J Child Neurol. 2007; 22:1069–78. [PubMed: 17890403]

6. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr. 2005; 146:453–60. [PubMed: 15812446]

7. Cuaycong M, Engel M, Weinstein SL, et al. A novel approach to the study of hypoxia-ischemia-induced clinical and subclinical seizures in the neonatal rat. Dev Neurosci. 2011; 33:241–50. [PubMed: 21952605]

8. Wyatt JS, Gluckman PD, Liu PY, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics. 2007; 119:912–21. [PubMed: 17473091]

9. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. J Pediatr. 2012; 161:88–93. [PubMed: 22306045]

10. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. Jama. 2000; 284:1417–24. [PubMed: 10989405]

11. Wu YW. Systematic review of chorioamnionitis and cerebral palsy. Ment Retard Dev Disabil Res Rev. 2002; 8:25–9. [PubMed: 11921383]

12. Schlapbach LJ, Aebischer M, Adams M, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics. 2011; 128:e348–57. [PubMed: 21768312]

13. Glass HC, Bonifacio SL, Chau V, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. Pediatrics. 2008; 122:299–305. [PubMed: 18676547]

14. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992–1995. Arch Pediatr Adolesc Med. 2000; 154:725–31. [PubMed: 10891026]

15. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. Jama. 2004; 292:2357–65. [PubMed: 15547163]

16. Shalak L, Johnson-Welch S, Perlman JM. Chorioamnionitis and neonatal encephalopathy in term infants with fetal acidemia: histopathologic correlations. Pediatr Neurol. 2005; 33:162–5. [PubMed: 16139729]

17. Bartha AI, Foster-Barber A, Miller SP, et al. Neonatal encephalopathy: association of cytokines with MR spectroscopy and outcome. Pediatr Res. 2004; 56:960–6. [PubMed: 15496611]

18. Barkovich AJ, Hajnal BL, Vigneron D, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. AJNR Am J Neuroradiol. 1998; 19:143–9. [PubMed: 9432172]

19. Miller SP, Latal B, Clark H, et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. Am J Obstet Gynecol. 2004; 190:93–9. [PubMed: 14749642]

20. Bonifacio SL, Glass HC, Vanderpluym J, et al. Perinatal events and early magnetic resonance imaging in therapeutic hypothermia. J Pediatr. 2011; 158:360–5. [PubMed: 20965514]

21. Newton ER. Chorioamnionitis and intraamniotic infection. Clin Obstet Gynecol. 1993; 36:795–808. [PubMed: 8293582]

22. Modi N, Dore CJ, Saraswatula A, et al. A case definition for national and international neonatal bloodstream infection surveillance. Arch Dis Child Fetal Neonatal Ed. 2009; 94:F8–12. [PubMed: 18499771]

23. Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics. 2010; 126:903–9. [PubMed: 20974782]

24. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics. 1999; 103:e77. [PubMed: 10353974]

25. Rutherford M, Ramenghi LA, Edwards AD, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. Lancet Neurol. 2010; 9:39–45. [PubMed: 19896902]

26. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med. 2010; 164:352–6. [PubMed: 20368488]

27. Vohr BR, Stephens BE, Higgins RD, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. J Pediatr. 2012; 161:222–8. e3. [PubMed: 22421261]

28. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. J Pediatr. 2012; 160:553–8. [PubMed: 22048046]

29. Hajnal BL, Sahebkar-Moghaddam F, Barnwell AJ, Barkovich AJ, Ferriero DM. Early prediction of neurologic outcome after perinatal depression. Pediatr Neurol. 1999; 21:788–93. [PubMed: 10593667]

30. Eklind S, Mallard C, Arvidsson P, Hagberg H. Lipopolysaccharide induces both a primary and a secondary phase of sensitization in the developing rat brain. Pediatr Res. 2005; 58:112–6. [PubMed: 15879289]

31. Brochu ME, Girard S, Lavoie K, Sebire G. Developmental regulation of the neuroinflammatory responses to LPS and/or hypoxia-ischemia between preterm and term neonates: An experimental study. J Neuroinflammation [online]. 201110.1186/1742-2094-8-55

32. Murphy DJ, Sellers S, MacKenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. Lancet. 1995; 346:1449–54. [PubMed: 7490990]

33. Grether JK, Nelson KB, Emery ES 3rd, Cummins SK. Prenatal and perinatal factors and cerebral palsy in very low birth weight infants. J Pediatr. 1996; 128:407–14. [PubMed: 8774515]

34. Neufeld MD, Frigon C, Graham AS, Mueller BA. Maternal infection and risk of cerebral palsy in term and preterm infants. J Perinatol. 2005; 25:108–13. [PubMed: 15538398]

35. Dammann O, Leviton A. Infection remote from the brain, neonatal white matter damage, and cerebral palsy in the preterm infant. Semin Pediatr Neurol. 1998; 5:190–201. [PubMed: 9777677]

36. Leviton A, Paneth N, Reuss ML, et al. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Developmental Epidemiology Network Investigators. Pediatr Res. 1999; 46:566–75. [PubMed: 10541320]

37. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA. 2003; 290:2677–84. [PubMed: 14645309]

38. Kuypers E, Ophelders D, Jellema RK, Kunzmann S, Gavilanes AW, Kramer BW. White matter injury following fetal inflammatory response syndrome induced by chorioamnionitis and fetal sepsis: lessons from experimental ovine models. Early Hum Dev. 2012; 88:931–6. [PubMed: 23078831]

39. Chau V, Poskitt KJ, McFadden DE, et al. Effect of chorioamnionitis on brain development and injury in premature newborns. Ann Neurol. 2009; 66:155–64. [PubMed: 19743455]

40. Harteman JC, Nikkels PG, Benders MJ, Kwee A, Groenendaal F, de Vries LS. Placental pathology in full-term Infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. J Pediatr. 2013; 163:968–975. [PubMed: 23891350]

41. Mallard C, Hagberg H. Inflammation-induced preconditioning in the immature brain. Semin Fetal Neonatal Med. 2007; 12:280–6. [PubMed: 17327146]

42. Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr. 2008; 153:170–5. 5 e1. [PubMed: 18534228]

43. Graham EM, Holcroft CJ, Rai KK, Donohue PK, Allen MC. Neonatal cerebral white matter injury in preterm infants is associated with culture positive infections and only rarely with metabolic acidosis. Am J Obstet Gynecol. 2004; 191:1305–10. [PubMed: 15507958]

44. Back SA. Perinatal white matter injury: the changing spectrum of pathology and emerging insights into pathogenetic mechanisms. Ment Retard Dev Disabil Res Rev. 2006; 12:129–40. [PubMed: 16807910]

45. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013; 1:CD003311. [PubMed: 23440789]
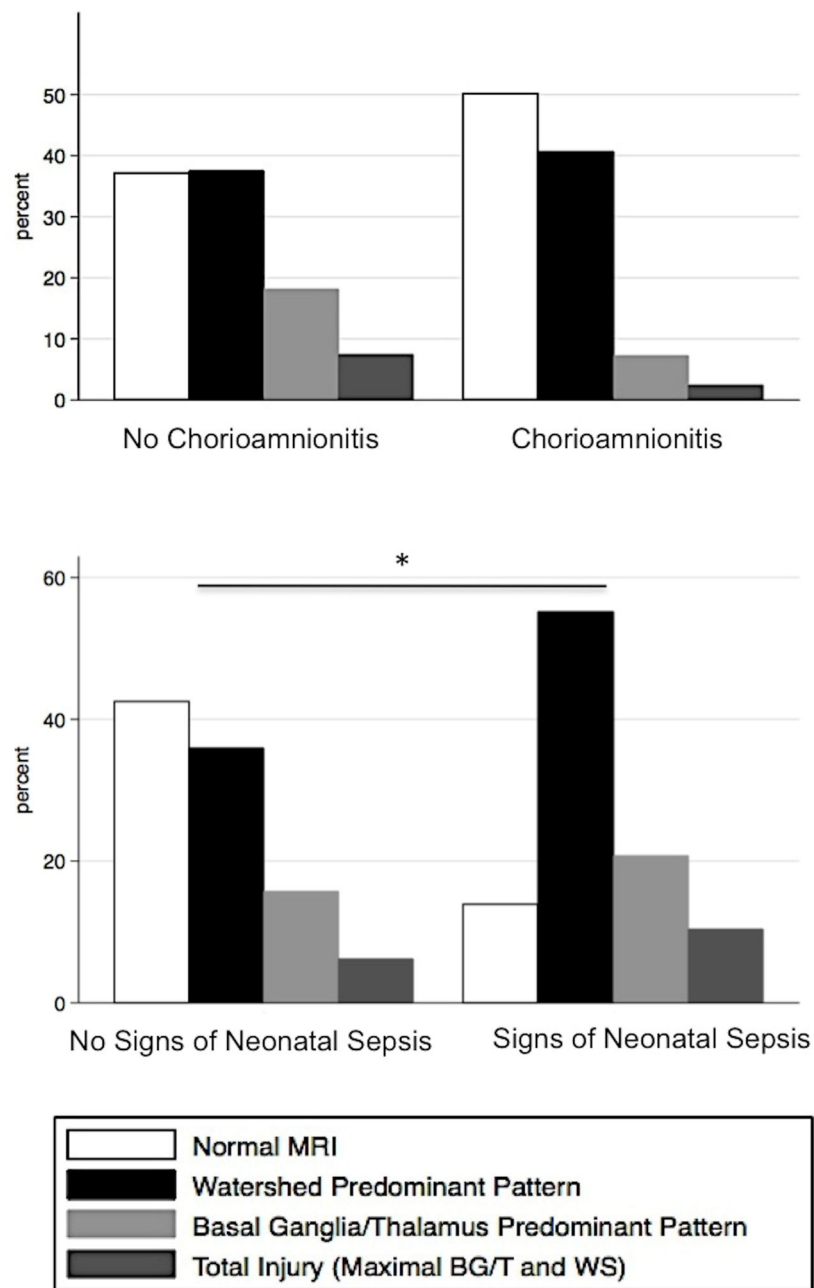
Figure 1.
Association between infection and categorical pattern of brain injury among 258 neonates with encephalopathy with and without maternal chorioamnionitis (A) and signs of neonatal sepsis (B) (χ^2). White indicates normal MRI, black, watershed predominant pattern of injury, and grey, basal ganglia/thalamus injury. *P=0.053; **P=0.007

Figure 2.
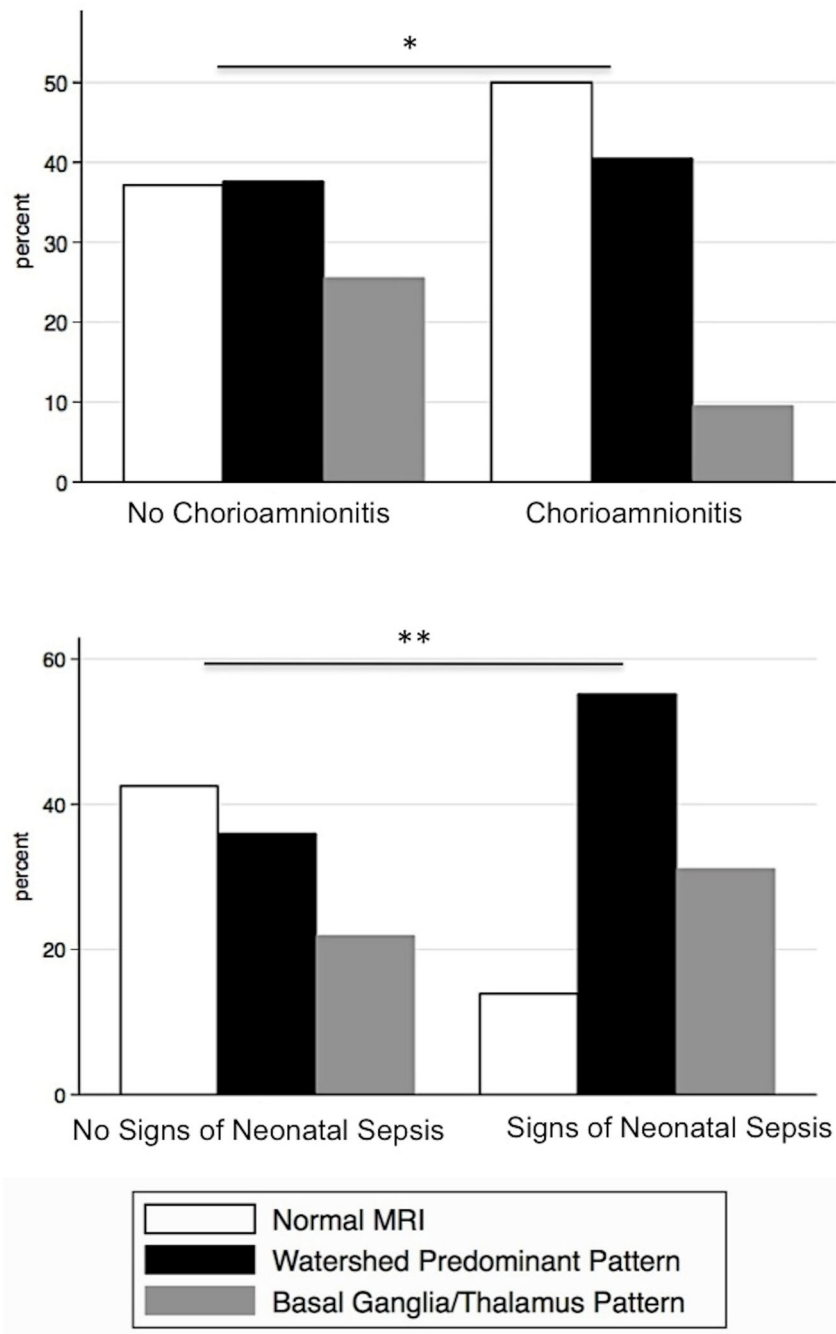Association between infection and categorical pattern of brain injury among 258 neonates with encephalopathy with and maternal chorioamnionitis (A) and signs of neonatal sepsis (B) (χ^2). White indicates normal MRI, black, watershed predominant pattern of injury, and grey, basal ganglia/thalamus injury, dark grey, total injury (i.e. maximal basal ganglia/thalamus and watershed scores). *P=0.03

Table 1

Patient characteristics of 258 subjects with neonatal encephalopathy.

	Chorioamnionitis N = 42[a]	Signs of Neonatal Sepsis N = 29[a]	No infection N = 193	P-value
Male sex	26 (62%)	14 (48%)	106 (55%)	0.4
Gestational age, wks	40.2 ± 1.3	39.7 ± 2.0	39.5 ± 1.7	0.09
Birth weight, g	3307 ± 522	3197 ± 666	3386 ± 596	0.4
Prolonged rupture of membranes >18hrs	18 (43%)	7 (24%)	27 (14%)	0.005
Emergent cesarean section	11 (31%)	16 (55%)	79 (41%)	0.1
1-minute Apgar score	2 (0, 7)	2 (0, 6)	2 (0, 8)	0.6
5-minute Apgar score	4 (0, 9)	4 (0, 9)	4 (0, 9)	0.2
pH	7.12 ± 0.17	7.02 ± 0.16	7.01 ± 0.19	0.006
Base excess	-8.3 ± 4.9	-14.0 ± 6.5	-13.3 ± 7.0	0.0008
Encephalopathy score (19)	4 (1, 6)	6 (1, 6)	4 (0, 6)	0.002
Neonatal EEG Seizures	13 (30%)	13 (45%)	73 (38%)	0.5
Hypothermia therapy	18 (43%)	8 (28%)	66 (34%)	0.5
Deceased	2 (5%)	4 (14%)	13 (7%)	0.4

[a] 6 subjects had both chorioamnionitis and signs of neonatal sepsis

Data are presented as N(%), mean ± SD or median (range)

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Table 2

Moderate or severe brain injury as seen on magnetic resonance imaging among 258 subjects with neonatal encephalopathy.

	N	Moderate- Severe Injury, n(%)	Unadjusted	Unadjusted P-value	Adjusted[a]	Adjusted P-value[a]
					OR (95% CI)	
Chorioamnionitis						
Yes	42	10 (24%)	0.3 (0.1–0.7)	0.003	0.3 (0.1–0.7)	0.004
No	216	107 (50%)	ref		ref	
Signs of Neonatal Sepsis						
Yes	29	17 (58%)	1.8 (0.8–4.0)	0.1	1.4 (0.5–3.5)	0.5
No	229	100 (44%)	ref		ref	

[a] Adjusted for maximal encephalopathy score and first pH

Table 3

Chorioamnionitis, signs of neonatal sepsis, and risk of neuromotor score (NMS) 2 and Bayley Scales of Infant Development (BSID) Mental Development Index (MDI) <70 or cognitive subscore <85 among children with neonatal encephalopathy.

	N	NMS 2, n(%)	OR (95% CI)			
			Unadjusted	Unadjusted P-value	Adjusted[a]	Adjusted P-value[a]
Chorioamnionitis						
Yes	19	2 (10%)	0.3 (0.1–1.3)	0.1	0.5 (0.2– 1.8)	0.3
No	107	31 (29%)	ref		ref	
Signs of Neonatal Sepsis						
Yes	14	8 (57%)	4.6 (1.5–14.6)	0.009	2.9 (0.9– 9.3)	0.07
No	112	25 (22%)	ref		ref	

	N	BSID II MDI<70 or Bayley III cognitive subscore <85, n(%)	Unadjusted	Unadjusted P-value	Adjusted[a]	Adjusted P-value[a]
Chorioamnionitis						
Yes	18	0	0	0.03	-	-
No	99	21 (21%)	21 (21%)			
Signs of Neonatal Sepsis						
Yes	12	4 (33%)	4 (33%)	0.1	1.8 (0.8–4.0)	4.8 (0.5– 41.9)	0.1
No	105	17 (17%)	17 (17%)		ref	

[a] Adjusted for maximal encephalopathy score and first pH