

# Is infection a factor in neonatal encephalopathy?

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In adults and in very preterm neonates, systemic infection is a well-recognised cause of encephalopathy. Although the manifestations of encephalopathy are very similar in the fetal inflammatory response and in acute hypoxic-ischaemic events, neonatal encephalopathy (NE) in term infants is more often attributed primarily to hypoxia-ischaemia rather than to infection. Is systemic infection an important etiological factor in NE in term and late preterm infants?

A striking 1999 case report<sup>1</sup> showed that placental infection with group B streptococcus can cause NE and that the clinical picture can closely mimic both immediate and later signs commonly assumed to indicate birth asphyxia. Many other reports describe associations of placental infections with encephalopathy in term neonates, suggesting that infection, or the resulting inflammation, can indeed underlie NE without an associated sentinel event causing asphyxia. This brief discussion considers the evidence of an infection-NE association, the difficulty of distinguishing infectious from non-infectious inflammation and the way forward.

Most of the evidence relating infection to NE has concerned infections identified during the admission for delivery, usually defined histologically in the placenta, or clinically. Histological evidence includes chorioamnionitis, which is inflammation on the maternal side of the placenta and funisitis on the fetal side, with infiltration of the umbilical cord with inflammatory cells. Clinical evidence of infection includes maternal fever in labour, uterine tenderness, purulent discharge or fetal tachycardia. A third approach to identifying placental infection is by microbiological evaluation. Unfortunately, results of these approaches are often not in agreement,<sup>2,3</sup> and multiple identification methods are rarely used in the same study.

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## HISTOLOGICAL CHORIOAMNIONITIS

McDonald *et al*<sup>4</sup> compared placentas of 93 infants with NE with placentas of normal term controls (n=816) and of random controls (n=387), finding funisitis in 31.2% of NE placentas versus 5.4% and 4.4% of controls (p=0.002). Chorioamnionitis and villitis were also significantly more frequent in NE, especially in more severe grades of histological inflammation. Vasculitis, endothelial damage, fibrin deposition and thrombus formation may occur as a consequence of severe infection. Reports subsequent to McDonald *et al*<sup>4</sup> have also associated severe placental inflammation involving fetal response with NE, especially if associated with thrombovascular lesions.<sup>5,6</sup> Milder inflammation without fetal response was not associated with NE.

In a population-based Canadian registry,<sup>7</sup> chorioamnionitis was more frequent in the 34% of term-born children with cerebral palsy (CP) who had had NE as newborns, as compared with those with CP who had not manifested NE.

Even infants admitted for therapeutic cooling, selected because their neurological dysfunction was thought to stem from acute asphyxial injury, had high rates of inflammatory placental lesions.<sup>8-10</sup> Histological chorioamnionitis is also associated with other risk factors for NE and CP, including low Apgar scores.<sup>11,12</sup> A recent study not finding histologic chorioamnionitis to predict NE in term infants did not describe severity of inflammation or presence of a fetal response.<sup>13</sup>

## CLINICAL CHORIOAMNIONITIS

Few large population-based studies of infection/inflammation and NE have had systematic placenta histology and therefore have employed clinical indicators as a surrogate. The most common indicator used is maternal fever in labour, associated in controlled studies with heightened risk of NE.<sup>14,15</sup> Clinical chorioamnionitis defined as maternal fever was twice as frequent as identified asphyxial birth events in neonates admitted for therapeutic hypothermia<sup>16</sup> and is a frequent antecedent of low Apgar scores.<sup>17,18</sup> Neonatal seizures are a common feature of NE; a clinical diagnosis of chorioamnionitis, other maternal infection and isolated fever were all

associated with increased risk of neonatal seizures.<sup>19</sup> Perinatal stroke has also been associated with intrapartum fever.<sup>20</sup>

Maternal fever in labour has many potential causes, including intrauterine or systemic infection, dehydration, muscular effort or epidural anaesthesia. Epidural anaesthesia is associated with lower Apgar scores and heightened risk of neonatal seizures.<sup>21</sup> Whether epidural-related fever is regularly accompanied by chorioamnionitis is not well agreed.<sup>22,23</sup>

In a large population-based study, clinical markers of inflammation were associated with a 5.6-fold increase in risk of clinically diagnosed hypoxic-ischaemic encephalopathy (HIE) in neonates with later-recognised CP.<sup>24</sup> Clinical markers, although neither sensitive nor specific for infection/inflammation, permitted the tentative estimate that these contribute about 10% of clinically diagnosed HIE in infants with CP and 3% of total CP.<sup>24</sup> Term neonates with inflammatory markers who were neurologically asymptomatic in the first days of life were not at increased risk of CP. NE appears to be on a pathway from infection/inflammation to CP.

## MICROBIOLOGICAL EXAMINATION

It is usually assumed that chorioamnionitis and funisitis are the results of infection by microorganisms that directly cause neonatal sepsis or produce injurious systemic inflammation. For example, in early onset neonatal group B streptococci infection, neurological symptoms are common even without evidence of meningitis.<sup>25</sup> In very preterm placentas, association with microbiological infection seems to be largely true, but for term placentas the evidence is weaker. Some reports have identified infective microorganisms in the placenta in NE, but culture-proven or histologically visible infection was rare in acute histological chorioamnionitis in placentas of term infants born to low-risk mothers.<sup>26</sup> Significantly, there were indications of an inflammatory state in these women before the birth.<sup>26</sup> It remains uncertain how much of the inflammation associated with NE is infectious in nature.

## NON-INFECTIOUS INFLAMMATION

Non-infectious inflammation in the placenta can apparently contribute to NE. The classic form of placental non-infectious inflammation is chronic villitis, defined by chronic inflammatory cells of maternal origin in fetal villi. In most cases, no infective organism is recognised and the condition is known as villitis of unknown aetiology (VUE). VUE is observed in about 10% of term placentas,

apparently related to breakdown of maternal tolerance for the fetoplacental unit as parturition approaches.

Several controlled studies link high-grade VUE with increased risk of NE<sup>4 6 10</sup> and with lesions on MRI imaging that are commonly attributed to asphyxial birth events.<sup>10</sup> VUE is also associated with risk factors for NE and for CP, including prior fetal loss, fetal growth restriction, non-reassuring fetal heart rate patterns in labour, emergency surgical delivery, and severe acidosis in the absence of a sentinel event.<sup>27</sup> VUE can thus mimic birth asphyxia and cannot be recognised without placental examination.

The link between NE and other non-infectious forms of inflammation, such as that related to maternal autoimmune disease, is largely unexamined.

## IMPLICATIONS

Placental lesions are common in NE, suggesting that antenatal infection, inflammation and/or vasculopathy occur in some or much of NE, including that clinically described as hypoxic-ischaemic. Reliance on analyses that do not evaluate evidence of infection/inflammation or severity of inflammation may lead to an exaggeration of the role of intrapartum asphyxia as a singular cause for NE.

Therapeutic cooling has led to decreased mortality and morbidity in neonates with NE, but unfortunately, only a minority of cooled babies benefit.<sup>28</sup> Neonatal hypothermia was designed as an intervention for acute asphyxial injury following a sentinel event. Might placental inflammation and/or vasculopathy in NE limit therapeutic response to cooling?<sup>29</sup> There is little evidence that cooling improves outcome in neonates with placental inflammation and/or vasculopathy; observations by Wintermark *et al*<sup>8</sup> and others suggest that it may not.

No biomarkers have yet been identified that are highly specific to infectious versus non-infectious inflammation. Of the biomarker panels that exist, few predict outcome sufficiently well for clinical use. 'To date, no microbiological test, clinical sign or scoring system, or laboratory marker is able to safely distinguish between infected and uninfected infants.'<sup>30</sup> Ubiquitous use of antibiotics is likely to continue in NE for the foreseeable future.

Might treatment targeting immune processes and inflammation benefit some neonates with NE? How will we identify them? In the near future, much of our information about infants with NE will

come from randomised trials that test cooling plus an additional therapeutic intervention (cooling+). Many of the adjunct medications being tested, such as erythropoietin and melatonin, have global anti-inflammatory properties in addition to their specific activities.<sup>31</sup> Only the collection of data on infection/inflammation in enrolled infants and prospectively planning secondary analyses in upcoming trials will provide information on whether these medications offer additional benefit and if their anti-inflammatory properties contribute usefully to management.

In addition, novel therapeutics being developed in preclinical models, such as neurosteroids, growth factors and unique anti-inflammatory agents, should be assessed in current experimental models that use hypoxia and/or ischaemia to mimic term or near-term NE, and in peripartum inflammation models and in combination models<sup>32</sup> that may better reflect the complexity of human NE.

Moving forward, cooling+ trials should incorporate information on placental histology, bacteriology and molecular markers of placental infection, along with maternal and family history. Secondary analyses in those trials could test the hypothesis that severe inflammation of the placenta with fetal response is associated with NE, and could attempt to distinguish infectious from non-infectious inflammation.

Recognising which depressed neonates have placental lesions, particularly funisitis and vasculitis which are highly associated with NE, may enable future cooling+ trials to focus on infants most likely to benefit, while seeking additional or alternative treatments for neonates with evidence of vasculopathy, infection or non-infectious inflammation.

**Contributors** KBN, a paediatric neurologist, wrote the main body of this article. AAP, a neonatologist and neuroscientist with special interest in the placenta, contributed a section and made useful suggestions concerning the remainder. AAP is partly supported by NIH Director's New Innovator Award (DP2OD006457).

**Competing interests** None.

**Provenance and peer review** Commissioned; externally peer reviewed.



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**To cite** Nelson KB, Penn AA. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F8–F10.

Received 10 June 2014

Revised 28 July 2014

Accepted 30 July 2014

Published Online First 28 August 2014

*Arch Dis Child Fetal Neonatal Ed* 2015;100:F8–F10.  
doi:10.1136/archdischild-2014-306192

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