

# Neonatal Encephalopathy

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## Take Home Message

Neonatal Encephalopathy may be caused by hypoxic ischemic insults or inflammatory insults and modified by innate protective or excitatory mechanisms. Understanding the underlying pathophysiology is important in formulating a rational approach to therapy.

## Introduction

Neonatology is a constantly evolving specialty. As our understanding of fetal and neonatal physiology and pathophysiology increase, our approach to therapy is modified and constantly refined. Approaches to therapy based on new ideas are introduced as those found to be based on incorrect assumptions are abandoned. One area currently undergoing reassessment is the pathogenesis of the neurologic disease and multiorgan maladaptation traditionally referred to as neonatal maladjustment syndrome. This discussion covers the neurologic aspect of that disease syndrome which I refer to as Neonatal Encephalopathy (NE).

## Pathogenesis

Currently the best evidence suggests that NE is a result of Septic Encephalopathy (SE), Hypoxic Ischemic Encephalopathy (HIE) or the interaction of the two, modified by innate protective mechanisms.<sup>1</sup> SE may be mediated by inflammatory mediators originating from maternal systemic inflammatory response syndrome (SIRS)<sup>2</sup> or from fetal inflammatory response syndrome (FIRS).<sup>2,3</sup> Maternal SIRS may be the result of maternal placentitis or other maternal inflammatory focus and FIRS is most commonly a result of fetal placentitis. Thus, both remote inflammation<sup>2</sup> such as extrauterine inflammation (SIRS), intrauterine inflammation (SIRS), fetal/neonatal inflammation (FIRS/SIRS) or local inflammation (neuroinflammation) will have the same effect (SE).<sup>3</sup> In fetal circulation proinflammatory cytokines, prostaglandins, or lipopolysaccharide<sup>4</sup> may change the blood brain barrier permeability<sup>1</sup> resulting in the “leak” of mediators into the brain or the mediators may attach to cytokine receptors in areas devoid of the blood brain barrier<sup>4</sup> resulting in up-regulation of proinflammatory cytokines<sup>4</sup> and activation microglia/macrophages<sup>4</sup> resulting in fetal brain SIRS (neuroinflammation). In central inflammation, microglia activation is a key feature, which will lead to the release of cytokines as well as trophic factors.<sup>4</sup> The neuroinflammatory response depends on level and mix of inflammatory messengers.<sup>2,4</sup> Low levels of messengers may result in “preconditioning” leading to protection for repeat exposure to higher levels of mediators or for hypoxic ischemic insults but more commonly the result is “sensitization” (sometimes referred to as negative preconditioning)

which makes the neonate more susceptible to the effects of repeat exposure of inflammatory messengers or to even mild hypoxic ischemic insults.<sup>1,4</sup>

The neuroinflammatory response may result in changes in dendritic structure, catecholamine homeostasis, neuronal and glial proliferation, CNS vulnerability to other insults and in some circumstances brain lesions.<sup>1,4</sup> These changes may result in cognitive limitations, behavioral problems, visuospatial difficulties as well as other signs we see in foals with NE.<sup>2,3</sup>

Previously NE has been thought to be almost exclusively caused by hypoxic ischemic insults. Indeed, many practitioners continue to refer to NE as HIE. However, there is little evidence that most neonates with NE have had a prenatal hypoxic ischemic insult.<sup>5</sup> In fact there is a better correlation of inflammatory insults and NE in neonates without overt evidence of birth asphyxia or early neonatal asphyxia.<sup>5,6</sup> We have found a significant connection between placentitis and the occurrence of NE.<sup>6</sup> The strength of the association supports the hypothesis that placentitis is a cause of NE in foals. There is no doubt that those neonates that have intranatal or post natal asphyxia such as prolonged stage 2 labor, cord compression, birth apnea or cardiopulmonary failure will have true hypoxic ischemic encephalopathy. Hypoxic ischemic insults are strong inducers of neuroinflammation. But it should be kept in mind that although all cases of NE may have similar clinical signs, as the etiology and thus the pathogenesis and response to therapy may differ, it may be dangerous to refer to them all as cases of HIE.<sup>5</sup>

High concentrations of neurosteroids, especially alloprenanolone, protect the brain during fetal life.<sup>7,8</sup> The placenta provides substrates allowing maintenance of high levels of alloprenanolone in the fetal brain. These high levels are largely responsible for the somnolence which subdues the fetus.<sup>8</sup> At birth, with the removal of the placental source, the levels drop rapidly, allowing the fetus to “wake up.”

Allopregnanolone and its synthetic analogues have marked anti-seizure actions and raise seizure threshold<sup>7</sup> and protect against neuroexcitatory toxicity. Inflammatory mediators and hypoxic ischemic insults are powerful inducers of brain production of allopregnanolones before and after birth. The placenta also secretes pregnenolone and pregnenolone sulphate into the fetal circulation. These steroids have an excitatory action in the brain. Passage of sulphated steroids across the blood brain barrier is slow compared with the suppressive steroids. Normally the fetus has a well formed blood brain barrier and sulphated steroids would not enter the fetal brain in sufficient quantities to influence excitability. But under the influence of fetal infection, compromise of the blood brain barrier may allow the entry of these sulphates causing adverse effects.<sup>7,8</sup> Similar effects may occur with hypoxic ischemic insults.<sup>8</sup>

So there is a complex interaction with remote or local sepsis initiating encephalopathy which may be exacerbated by even mild hypoxic ischemic insults or by the entrance through the damaged blood brain barrier of excitatory sulfated steroids or inflammatory mediators. In addition, these processes simultaneously induce high levels of neuroprotective allopregnanolones. Loss of placental precursors at the time of birth may lead to decreased brain neurosteroid levels resulting in a window of increased vulnerability.<sup>7,8</sup> But the accompanying stress leads to increase in adrenal steroidogenesis leading to the release of neurosteroid precursors (deoxycorticosterone e.g. DOC) replacing the placental supply of precursors to the

CNS. This may restore the appropriate balance of neurosteroid action in the brain after birth and the transition from largely allopregnanolone before birth to allopregnanolone and TH-DOC (5 $\alpha$ -tetrahydro-deoxycorticosterone) mediated neuroprotective pathways after birth.<sup>7,8</sup> Adrenal insufficiency may lead to a decrease neurosteroid availability allowing more severe NE.<sup>8</sup> The protective effect of neurosteroids may result from GABA<sub>A</sub> receptor-mediated post-synaptic hyperpolarization<sup>7,8</sup> and interfering with glutamatergic transmission<sup>8</sup> with an overall effect of reducing excitation.<sup>7</sup>

These interactions can explain the common clinical observation that foals with NE secondary to placentitis may initially appear normal, followed by development of clinical signs often associated with excitation (constant activity, hyper-responsiveness, hypertonus) followed by onset of seizure-like activity and finally followed by a period of somnolence and recovery. Before and just after birth the effects of NE may be dampened by placental derived neurosteroids. As the neurosteroid levels wane, the clinical signs of NE emerge culminating in tonic clonic seizure-like activity. The stress of the disease induces adrenal steroidogenesis providing precursor for neurosteroids production and the neuroinflammatory response induces high levels of neurosteroids production resulting in protective somnolence and recovery. Foals with severe placental damage secondary to widespread placentitis may have less placental steroidogenesis and lower levels of protective neurosteroids or inflammatory mediator induced blood brain barrier deficits allowing sulphated steroids access to the CNS. In either case early onset of clinical signs, prenatal or intranatal, or more commonly within an hour of birth could be expected to occur. Although this pathogenesis is purely speculative, it could have significant therapeutic implications with the development of neurosteroids anesthetics.

## **Clinical Signs**

The neurologic signs seen in NE are remarkably similar between cases following predictable patterns even though all cases do not necessarily encompass all possible signs. The neurologic disease of neonatal foals not only involves behavioral abnormalities but also other neurologic signs including changes in respiratory patterns/function, changes in muscle tone, changes in responsiveness, vestibular signs and autonomic disruption (loss of vascular control, loss of thermoregulation, inappropriate bradycardia, etc.).

Foals with NE may show changes in responsiveness, muscle tone, behavior, evidence of brain stem damage or seizure-like behavior. Changes in responsiveness include hyperesthesia, hyperresponsiveness, hyperexcitability, hyporesponsiveness, periods of somnolence or unresponsiveness. Often foals go through a period of increased responsiveness followed by a period of decreased responsiveness. Changes in muscle tone include increased extensor tonus, hypotonia and other less common changes such as neurogenic myotonia or failure to protract front or hind legs. Changes in behavior are very common and include loss of suckle response, loss of tongue curl, loss of tongue coordination, disorientation especially relative to the udder, aimless wandering, loss of affinity for the dam and abnormal vocalization. Although blindness is commonly assumed based on collisions with obstacles, I find that most foals can see but don't process what they see and thus run into obstacles. Foals with NE commonly have changes in respiratory patterns with central tachypnea, apneusis, apnea, cluster breathing, ataxic breathing, Cheyne-Stokes breathing or central hypercapnia. Other signs of brain stem damage include loss

of thermoregulatory control, generalized weakness, anisocoria, pupillary dilation, pinpoint pupils, central hypotension, inappropriate bradycardia (autonomic disruption), decreased responsiveness, difficult to arouse, loss of consciousness, vestibular signs (circling, head tilt), facial nerve paresis and a variety of other signs. Foals with NE have a wide variety of signs and degrees of severity. More than 90% of affected foals are normal within 10 days.

Foals may also develop Neonatal Nephropathy (NN). There is a wide spectrum of disease seen in cases of NN including incomplete transition from fetal renal physiology, water/sodium retention, mild tubular dysfunction (sodium wasting), abnormal excretion of drugs (e.g. high amikacin trough levels), acute tubular necrosis or decreased GFR. Often the signs of dysfunction are subtle and easily overlooked unless anticipated. Although almost always transient, on occasion significant acute damage may lead to chronic renal disease. These foals often have a decreased GFR as reflected by a slow decrease birth creatinine or decreased creatinine clearance, delayed water excretion with edema formation and weight gain and slow response to fluid challenges.

Neonatal Gastroenteropathy (NG) can be manifested by a wide spectrum of signs ranging from mild indigestion with dysmotility and enema dependence to moderate disease with ileus, diapedesis of blood into the lumen and mucosal edema to severe disease with epithelial necrosis, intussusceptions, strictures, hemorrhagic gastritis/enteritis/colitis, and pneumatosis intestinalis. Even mild forms predispose to sepsis and SIRS with increased likelihood of translocation of bacteria. Like NN, often the signs of dysfunction are subtle and easily overlooked unless anticipated. The most common manifestation is dysmotility with meconium retention and lack of fecal passage for days (range 2-30 days). Despite fecal retention, an important aspect is lack of discomfort. Classically, foals with dysmotility will not return enema fluid or strain associated with rectal distension.

Often, affected foals have the triad of NE, NN and NG. Other problems seen include metabolic maladaptation, autonomic failure and other systemic problems. Most of these foals have no clear history of an intrauterine hypoxic ischemic insult but certainly have had some intrauterine challenge. This intrauterine challenge may be fetal inflammation and not always fetal hypoxia ischemia. There is a connection between placentitis and many neonatal diseases and there is a protective effect of treatment.<sup>6</sup> For many years I have suspected that the occurrence of placentitis is important in predisposing to these neonatal diseases.

## **Therapy**

So how should we treat foals with this complex syndrome? As we have no evidence based information on therapy of foals with NE, treatment of the disease is largely based on traditions and beliefs. Beliefs are usually based on rational extrapolation of information gleaned from experimental models and clinical trials in man. But as we have no solid evidence, treatment is somewhat arbitrary and there are no right or wrong approaches. As intrauterine insults appear to result in “sensitization” resulting in even mild hypoxic ischemic insults causing significant exacerbation of NE, my main goal is to support cerebral perfusion and oxygen delivery. This is achieved by insuring volemia with careful fluid replacement, use of inopressor as needed and insuring oxygen delivery by maintaining pulmonary oxygen loading and avoiding anemia. It is also vital to prevent catabolism by careful nutritional management. These goals should be

achieved by delivering intranasal oxygen insufflation when necessary, enhancing pulmonary gas exchange with postural support, maintaining hematocrit above 20%, maintaining perfusion as above, supplying adequate exogenous glucose initially and if enteral nutrition is not possible within 24 hours, parenteral nutrition. So these foals may need fluids (be careful to avoid fluid overload), oxygen, glucose and occasionally inotropes and pressors.

There have been a number of other favorite therapies used and although I have tried many, I have never been overly impressed and I feel we have little rationale grounded in evidence for most of them. With a recovery rate of 85-90% with supportive care alone, any additional therapy would have to be very good or significantly shorten the course to make its use worthwhile. Free radical scavengers (DMSO, mannitol) have been used to minimize reperfusion injury, and they may be appropriate within minutes after relieving a dystocia during birth resuscitation but if treatment is not given within an hour of the insult it will not help. Clinicians often treat cerebral edema that “must be present.” My experience parallels that of MDs who note that cerebral edema, when present, is an epiphenomena. It is a byproduct of severe disease and not part of the genesis. In survivable disease it doesn't seem to play a role. When a hypoxic ischemic insult is the cause, it may result in cellular edema and not cerebral edema unless it is very severe and the primary damage is fatal. Many clinicians use DMSO or mannitol routinely. I stopped using these treatments more than a decade and a half ago. I did look back at about 300 cases and found using no treatment was as effective or even a little better as gauged by survival to discharge than using either of these drugs. Thiamine has been used for its cerebral protective effect, but I don't think it aids recovery. Its supplementation is probably more useful as an aid to metabolism when high levels of dextrose are given especially in the face of hypermetabolism which sometimes accompanies severe sepsis.

A current favorite treatment of NE in foals is  $MgSO_4$  administration, however, its efficacy is unproven and  $MgSO_4$  may in fact be contraindicated. The  $MgSO_4$  story is very interesting. It was originally suggested as a therapy to prevent NE in babies when a retrospective study showed that women with preeclampsia who were treated with  $MgSO_4$  near the end of their pregnancy had a lower risk of having babies with NE.<sup>9</sup> Its possible therapeutic use was bolstered by the knowledge that it will block Ca channels which will in theory prevent neurocyte damage secondary to hypoxic ischemic insults. However, several prospective therapeutic trials of the use of  $MgSO_4$  in late pregnancy in women have found that the use of magnesium increases the risk of severe neurologic disease in babies.<sup>9</sup> It is actually preeclampsia which has the protective effect and not the  $MgSO_4$ .<sup>10</sup> Prenatal exposure to  $MgSO_4$  results in an increase in relative risk of neonatal death by 10.7 times (95% CI 2.9–18.5%; P 0.02; MagNet trial)<sup>11</sup> and results in decreased cerebral perfusion during the neonatal period.<sup>12</sup> The toxic effect may be mediated by  $SO_4$  and it is possible that in smaller doses of Mg or other Mg salts may have a protective effect against damage caused by hypoxic ischemic insults but in using it in foals we are not sure what dose might be toxic and which may be protective and as in human medicine, I have questioned how many foals with NE actually suffer from a hypoxic ischemic insult.<sup>5</sup> So I no longer use  $MgSO_4$  to treat NE (*primum non nocere*).

With the recent idea that the underlying etiology may be FIRS it is logical to consider anti-inflammatory drugs. As I believe that the insult occurs during the prenatal period that is when I concentrate anti-inflammatory therapy in cases where there is evidence of placentitis or other

inflammatory disease in the mare. In an observational retrospective study of the relationship between occurrence of placentitis and neonatal diseases including NE we found that treatment of the mare for placentitis appeared to protect against development of these diseases.<sup>6</sup> But using anti-inflammatory drugs after birth is likely to be too late and the possible adverse effects of these drugs outweighs the possible benefit in my opinion.

Seizure-like activity should be prevented to minimize the possibility of ongoing damage. Phenobarbital is my standard therapy despite its side effects which if anticipated can be minimized. Phenobarbital will cause a drop in core body temperature, a decrease in respiratory drive sometimes inducing hypercapnia, exacerbate pharyngeal collapse when present and it may potentiate hypotension resulting in deterioration of perfusion. All of these side effects can be minimized by early intervention. Small doses of phenobarbital (2-3 mg/kg) can be given repeatedly until seizures are controlled, infused over 15-20 minutes with a peak activity at 45 minutes. Once the seizures are controlled, in rare cases it may be necessary to repeat the dose in 6 to 12 hours. The half-life of phenobarbital in some foals may be >200 hours (others may have faster clearance) making maintenance unnecessary and even contraindicated. The degree of sedation achieved may be prolonged but usually the foal “wakes up” before the blood level drops probably because after recovery of the blood brain barrier it begins to exclude the drug. Recently it has been suggested that midazolam might make a better choice. I have not adopted this therapy primarily because it is my goal to insure cerebral perfusion and midazolam decreases cerebral perfusion and cerebral oxygen delivery soon after administration.<sup>13,14</sup> There is enough concern about adverse effects of midazolam in human neonatology that it has been recommended that it only be used in experimental trials.<sup>15,16</sup> Similar cautions have been raised about the use of ketamine in neonates, although there remains much controversy.<sup>16,17</sup> My feeling again is *primum non nocere*.

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