Neonatal Syndrome

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In the 1960's veterinarians recognized that some foals showed unusual behavioral traits soon after birth. They would "forget" how to nurse or never learn they often wandered compulsively, they lost affinity for the mare and seemed attracted by and bond to people. They sometimes seemed blind and often would hang their tongue out of the side of their mouth and seemed to be unaware of how to control it. They sometimes vocalize abnormally making sounds that mimicked a barking dog. These foals were referred to as "barkers," "wanderers" or "dummy" foals. In the early 1970's the term "neonatal maladjustment syndrome" was coined (NMS) to describe these foals and continues to be in popular use today. During the past 2 decades we have come to realize that the behavioral abnormalities are the tip of the iceberg. Not only are there a large variety of other neurologic signs, the syndrome often includes dysfunction of multiple organ systems. In the early 1990's veterinarians began to realize that the neurologic manifestations of these foals resemble those seen in other species suffering from experimental hypoxic ischemic insults. It became popular to refer to the neurologic signs as Hypoxic Ischemic Encephalopathy (HIE) and the multiorgan involvement as Perinatal Hypoxic-Ischemic Disease or Perinatal Asphyxia because of the suspected underlying etiology. In the mid 1990's evidence began to accumulate that a major cause of prematurity and neurologic damage in the neonate was associated with placental inflammatory disease. Neonatologists began to question whether or not all babies with neurologic signs had a hypoxic ischemic insult or if in some the insult was a direct result of inflammatory mediators. This lead to the use of Neonatal Encephalopathy (NE) as a generic term describing the age group and organ system disrupted but without suggesting an etiology ("-pathy" meaning any abnormality independent of etiology as apposed to "-itis" which refers to inflammation, etc.). NE includes HIE as well as other underlying etiologies such as inflammatory disease. I have adopted this terminology to describe all of the organ dysfunction we see since the etiology is unclear. Thus the renal manifestations are referred to as Neonatal

Nephropathy and the GI manifestations as Neonatal Gastroenteropathy, etc. I don't like the term NMS since maladjustment connotes behavioral abnormalities (in the mental health professions, an inability to cope with the problems and challenges of everyday living) whereas the neurologic manifestations we see in this disease are much more extensive.

Historically some investigators felt that all neonates experience some degree of intrapartum asphyxia. The theory was that during uterine contractions, the maternal placenta was poorly perfused resulting in progressive asphyxia. In fact, it was suggested that some degree of asphyxia is important in stimulating the transition from uterine to extra-uterine life. More recently investigations have shown minimal changes in fetal blood gases during normal parturition, bringing into question how much asphyxia does in fact occur during parturition. Traditionally it was thought that neonatal diseases were a result of intrapartum hypoxic-ischemic events. It is now accepted that the events leading to neonatal diseases may occur during prenatal, intrapartum and neonatal periods. These events may be a direct result of hypoxic ischemic asphyxial insults or inflammatory mediators. Inflammatory mediators are thought to have an important direct effect on fetal or neonatal organ systems which may potentiate milder hypoxic ischemic insults. It is likely that the summation of insults is as important as any particular insult (see Palmer - Neonatal Encephalopathy AAEP Focus Meeting 2008). Signs may occur at birth, but commonly are delayed for 12 to 18 hours.

The neurologic consequences of hypoxic-ischemic disease have been extensively studied. Uncomplicated hypoxemia, no matter how severe, does not cause brain damage largely because the redistribution and preferential blood flow to the heart and brain. Isolated cerebral ischemia without preexisting hypoxemia does not seem to produce significant neurologic lesions. The combination of systemic hypoxemia and regional ischemia results in significant damage. If hypoxia is severe enough, peripheral tissues develop oxygen debt leading to anaerobic glycolysis and production of a lactacidosis. The lactic acid diffuses into the blood causing a metabolic acidemia. The

acidosis depresses cardiovascular function resulting in ischemia. Ischemia not only results in hypoxia but also lack of delivery of other substrates. The result is hypoxic-ischemic disease.

A prolonged episode (1 to 4 hours) resulting in severe hypoxemia such as reduced uterine blood flow from maternal cardiovascular compromise may result in a combined respiratory and metabolic acidosis resulting in fetal cardiovascular compromise leading to ischemic insults.

Hypoxic-ischemic brain damage results in selective neuronal necrosis. This damage evokes a process that requires hours to days to produce gross and microscopic evidence of the underlying tissue disruption. Therefore some cases won't live long enough for lesions to become evident.

There are a number of causes of the severe hypoxemia needed to produce hypoxic-ischemic disease. *During the prenatal period:* reduced maternal oxygen delivery capacity (maternal anemia, maternal lung disease resulting in hypoventilation/hypoxemia, maternal cardiopulmonary disease); reduced uterine blood flow (maternal hypotension associated with endotoxemia or colic, maternal hypertension associated with laminitis and other painful conditions, abnormal uterine contractions leading to increased uterine vascular resistance); placental diseases (premature placental separation, placental insufficiency as with twins, placental dysfunction as with fescue toxicity or postmaturity, placentitis, placental edema); reduced umbilical blood flow (general anesthesia of the pregnant mare, congenital cardiovascular diseases, umbilical vessel occlusion, abnormal uterine contractions, inappropriate blood distribution in the fetus, fetal hypovolemia).

During the intrapartum period: dystocia; premature placental separation; uterine inertia; oxytocin induction of labor; c-section (general anesthesia, poor uterine blood flow due to

maternal positioning, reduced maternal cardiac out put, reduced umbilical blood flow, effects of anesthetics on fetus); anything that prolongs stage 2 labor.
During the neonatal period: prematurity; any reason for recumbency (musculoskeletal disease, sepsis, prematurity, mild hypoxic ischemic syndrome); pulmonary disease (meconium aspiration syndrome, milk aspiration pneumonia, persistent fetal circulation, septic pneumonia); severe recurrent apneic episodes or abnormal respiratory patterns; septic shock; anemia (neonatal isoerythrolysis, excessive umbilical bleeding, fractured ribs or femur); congenital cardiovascular disease.

The possible inflammatory etiology of these diseases is almost exclusively linked to placentitis. Experimental models of intrauterine infection during the last trimester show that the fetus develops neurologic lesions independent of pathogens. The inflammatory response of the placenta (fetal membranes) appears to be responsible for the neurologic disease. In a recent retrospective study we found a very strong correlation between placentitis and the development of NE, NN and NG in foals. In fact there seems to be a strong protective effect associated with prepartum treatment of placentitis in the mare. Foals from those mares are much less likely to have NE, NN or NG. It does not appear that neonatal inflammation (sepsis) has the same effect but it has not been studied.

The severity of disease and organs affected depend not only on the severity of the insult (whether hypoxic-ischemic, inflammatory or both) but also the duration of the insult, whether or not repeat insults occur (either the same type or different types, e.g. inflammatory or hypoxic ischemic or other insult) and when the insult occurs relative to fetal or neonatal development. Because of the large number of variables, there can be a wide variety of clinical presentations. All organ systems may be involved but in the neonatal foal, the most common signs originate from the CNS, the kidneys, the GI tract, the cardiovascular system, the lungs and the liver (in that order).

The signs of central disease are the most common and most noticeable abnormalities. When a foal experiences a high-risk situation damage may not necessarily occur. The relative resistance of some neonates to damage probably has to do with better executed adaptive mechanisms. Mild hypoxia results in redistribution of blood flow to critical tissues. If successful, this may result in prevention of damage. The inflammatory response is very complicated but also may be modified resulting in variable results. The fetal and neonatal inflammatory response is very different from the adult response. There are modifications so that growing tissues are protected from counterproductive damage, especially apoptosis while still targeting the pathogen. These modifications are incompletely understood but likely are the key to understanding the variable response to what seems to be the same insult.

Any combination of neurologic signs from a finite list of possibilities may develop because of the selective nature of the damage. The signs fall into the following categories: changes in responsiveness, changes in muscle tone, changes in behavior, signs of brain stem damage or seizure-like behavior/coma. Changes in responsiveness include: hyperesthesia, hyperresponsiveness, hyperexcitability, hyporesponsiveness, periods of somnolence and unresponsiveness. Changes in muscle tone include: hypotonia, extensor tonus, neurogenic myotonia. Changes in behavior 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, abnormal vocalization (" barker"). Signs of brain stem damage include: changes in respiratory patterns (hypercapnia, apnea, tachypnea, cluster breathing, etc.), loss of thermoregulatory control, anisicoria (3rd nerve, one side), pupillary dilation (midbrain), pinpoint pupils (pontine), hypotension, loss of consciousness (reticular formation), vestibular signs. Seizure-like behavior includes: marching type behavior, abnormal extensor tone, tonic-clonic seizures. Coma may develop followed by death.

The kidneys seem to be the second most common target of hypoxic disease in the equine. The most common presenting signs are oliguria or anuria. Often this is *not*

accompanied by a significant rise in creatinine early in the course. If the disease is mild, this problem is transient and easily corrected. There may be failure to make the transition from fetal renal physiology to neonatal physiology, mild to severe tubular dysfunction, glomerular disease, SIADH or a combination of problems. Often the renal compromise makes it difficult for the neonate to handle fluid load loads and frequently results in Na wasting. Since neonates usually highly conserve Na making sodium overload from fluid therapy a constant threat, the development of Na wasting in the urine, reversing this trend, makes Na balance a challenge for the clinician. Only rarely will significant renal disease result in irreversible damage or chronic renal disease result in renal failure.

The third most common target for hypoxemia is the gastrointestinal tract. The GIt is especially susceptible to damage when metabolic demands caused by digestion of food are superimposed on hypoxemic episodes. The signs associated with hypoxic damage may vary: mild indigestion, failure to absorb colostrum efficiently, dysmotility, ileus, diapedesis of blood into the lumen, epithelial necrosis, development of intussusceptions or strictures, hemorrhagic gastritis or enteritis/colitis. Hypoxic bowel disease may be an important predisposing factor in development of sepsis and SIRS secondary to translocation of bacteria through the GI tract.

Other target tissues include the cardiovascular system resulting in lack of response of peripheral vessels to endogenous and exogenous adrenergic agents and cardiovascular collapse resulting in refractory shock. Arrhythmias secondary to focal cardiac lesions are also common. Significant pulmonary damage may occur and a reversion to fetal circulation may be easily induced resulting in more severe asphyxia. More rarely the liver may be a target and mild to severe hepatitis may result. At times damage to the tissues results in induction of SIRS. Once SIRS develops it may be impossible to reverse and is commonly the cause of fatalities in these cases. Fortunately it is unusual to have such severe damage. Approximately 90% of foals suffering from Neonatal Syndrome will recover if given proper supportive care.

Therapy

Control of seizures: It is extremely important that seizures be controlled. Although neonatal neurocytes are very resistant to acute damage caused by seizures, the muscle activity of a grand mal seizure will increase oxygen demand of tissues and decrease ventilation efficiency setting the foal up for a hypoxic ischemic episode. Diazepam can be used for emergency control of seizures, but if more than 2 seizures occur, phenobarbital should be given to effect. It should be kept in mind that the blood half-life of phenobarbital in premature foals may be 200 hours or longer. So whatever blood level you finally achieved you may have to live with for quite awhile. However, phenobarbital should be given repeatedly until seizures are controlled. If phenobarbital fails, phenytoin may be tried. Recently some clinicians have used midazolam either as boluses or by continuous infusion. Since midazolam has been showed to consistently cause a transient decrease in cerebral perfusion followed by what appears to be a change in perfusion priorities in the brain and since there have been a number of adverse reactions in human neonates, I have not used this drug. The most important consideration in treating neonatal encephalopathy is maintaining cerebral perfusion. I also feel that ketamine and xylazine should be avoided in these neonates since these drugs will cause cerebral hypertension. In human neonates a CRI of lidocaine has been successful in controlling otherwise refractory seizures. During seizures it is also important to protect the foal from injury.

General cerebral support: The most important therapy is maintaining cerebral perfusion. This is achieved by careful fluid replacement to ensure adequate fluid loading but not overloading and by maintaining adequate blood pressure through the combined use of inotropes and pressors. Only in the most severe cases is true cerebral edema present. Primarily the lesion is cellular edema. Occasionally we use thiamine to support the metabolic processes that may decrease cellular edema, however efficacy is completely unproven. Some clinicians routinely use drugs such as mannitol or DMSO. Over the

past 15 years I have used very little DMSO or mannitol and I have seen no difference in outcome of these cerebrally challenged cases.

Correcting metabolic abnormalities: These foals often have a variety of metabolic problems including hypoglycemia/hyperglycemia, hypocalcemia/hypercalcemia, hypokalemia/hyperkalemia, hypochloremia/hyperchloremia, and various degrees of metabolic acidosis. These problems should be addressed, however the normal hypoglycemic period and the common finding of hypocalcemia without other signs should be taken into account.

Maintain blood gases: Foals suffering from perinatal asphyxia often have recurrent bouts of hypoxemia and occasionally hypercapnia. We have traditionally felt that these problems need to be treated or further damage will occur and a downward spiral will ensue. However there is now good evidence that mild hypercapnia and mild hypoxemia may be beneficial and permissive hypercapnia and hypoxemia have been induced for their therapeutic effect. The tipping point between benefit and detriment has not been defined so although I may not be as quick to intervene or as aggressive in my intervention as in the past, I still act on these problems. Treatment with intranasal oxygen and occasionally caffeine or positive pressure ventilation may be required. Blood pH should be corrected and maintained in a near normal range. Occasionally a significant metabolic alkalosis develops requiring tolerance of marked hypercapnia. This should be attacked by attempting to correct the cause of the metabolic alkalosis and not by ventilation and lowering the CO_2. The goal is to have the pH approach normal.

Many foals with Neonatal Syndrome will suffer from neonatal encephalopathy resulting in depression of central respiratory receptors. Although these foals are good candidates for transient mechanical ventilation, some will respond adequately to respiratory center stimulants. Caffeine may adequately stimulate respiration. The serum half-life of caffeine in human neonates is very variable making the

pharmacodynamics difficult to predict. Therapeutic trough serum concentrations in human neonates are between 5 and 25 µg/ml with toxic reactions seen above 40 µg/ml. Limited experience in foals indicates that trough blood levels range between 4 and 10 µg/ml. Treated foals have an elevated level of arousal and become more reactive to environmental stimuli. Adverse reactions include restlessness, hyperactivity and tachycardia. Caffeine therapy will fail if the hypercapnia is a response to metabolic alkalosis and the pH is not low. Critically ill neonatal foals commonly develop electrolyte imbalances that result in metabolic alkalosis as explained by the strong ion difference theory. These foals will develop a secondary hypercapnia in an effort counteract the alkalosis. This physiologic response should be treated by correcting the electrolyte abnormalities and not by manipulating the respiratory system with drugs or mechanical ventilation.

Maintain tissue perfusion: It is extremely important to maintain tissue perfusion and oxygen delivery to tissues to avoid further damage. Oxygen carrying capacity of the blood should be maintained by maintaining an adequate PCV with transfusions if necessary. Adequate plasma volume should also be maintained while simultaneously taking care not to fluid overload the patient. This is important since fluid overloading could lead to cerebral edema and edema of other tissues such as the GI tract which may exacerbate damage in these areas by interfering with oxygen delivery. It also may lead to pulmonary edema and less efficient gas exchange and cardiac edema leads to poor cardiac output. Perfusion should be maintained through adequate cardiac output and blood pressure. It should be clearly understood that there is no magic blood pressure value to aim for. Instead adequate perfusion is the goal as reflected by maintaining urine output, perfusion of the limbs, perfusion of they brain as reflected by improved mental status, perfusion of bowel as indicated by normal GI function, etc. Often these foals require inotrope and pressor therapy. Occasionally the hypoxic or septic damage is severe enough that the vessels do not respond to these drugs and alternatives are required.

Maintain renal function: The kidney is a target for hypoxic and septic damage. The signs may be associated with disruption of normal renal blood flow or tubular edema progressing to acute tubular necrosis. It is important to balance intake with urine output to ensure that fluid overload does not occur. Early signs of fluid overload include development of ventral edema especially between the front legs and distally on the limbs. Edema may occur in other organ systems but is difficult to detect clinically. The most sensitive way to detect fluid overload is through detecting non-nutritional weight increases. Daily or more frequent weight measurements are important in the clinical management of the neonate. Pulmonary edema is a late sign and is more commonly associated with loss of vascular integrity rather than fluid overload. If present it can lead to interference with gas exchange and decreased compliance leading to respiratory distress and failure. Cerebral edema is also a late sign and likewise is more frequently associated with vascular injury but can result in exacerbation of central signs which should alert the clinician to possible of terminal fluid overload. Although there appears to be little role of dopamine or furosemide in protecting the kidney or reversing kidney damage, these drugs will enhance urine output and can be useful in fluid overload situations. It is not important to transform oliguric renal failure into a condition where higher urine output is present. When it is mistakenly believed that it is, over use of these drugs may drive a diuresis requiring fluid replacement and can be counterproductive. Conservative use of these drugs is currently our routine. Low doses of dopamine may result in a natriuresis. Furosemide may be given as boluses or as a continuous infusion. Once furosemide diuresis begins attention must be paid to electrolyte balance since loss of K, Cl and Ca can be significant and metabolic alkalosis commonly develops.

Treatment of GI dysfunction: Hypoxic and septic damage to the gastrointestinal tract may result in a variety of clinical signs. Continued feeding in the face of episodes of hypoxemia and ischemia may result in further damage. For this reason oral feeding must be undertaken with great care and often full nutritional requirements cannot be met enterally. In such cases partial parenteral nutrition is extremely valuable and

commonly used. The damage to the GI tract appears to lag behind other tissues and the true extent may not be known for several days to a week. Over zealous use of prokinetics with poor motility appears to predispose to more damage and intussusceptions. My general philosophy is to let the GI tract tell me when it is ready and not to try to force it to work more efficiently. Dysmotility is the most common clinical sign resulting in retention of meconium and failure to pass feces for a prolonged time. Sometimes this period may be weeks but most often it is 4 to 7 days. Full enteral feeding may not be possible until the resolution of the dysmotility as indicated by regular fecal passage. Special attention to passive transfer and glucose homeostasis is required in cases with neonatal enteropathy.

Recognition and early treatment of secondary infections: These foals are very susceptible to secondary infections and almost universally develop them. They should be monitored closely for localizing signs of infection and repeated blood cultures should be obtain in an attempt to isolate an etiologic agent. Close attention to culture and sensitivity results from isolates from this patient and the past history of nosocomial pathogens of the NICU should direct antimicrobial therapy. Also repeat measurements of IgG should be made and repeat plasma transfusions may be required. Nosocomial infections may be rapidly overwhelming and deterioration of the clinical course should raise the suspicion of such secondary problems.

General supportive care: General nursing care is very important in these individuals to prevent secondary problems and to speed recovery. A clean, dry, thermally regulated environment is important. Frequent position changes and physical therapy is also important. Close attention to details such as fecal production, urine production and changes in attitude can be very important in the management of these cases.

Prognosis: Prognosis is variable in these cases and depends on the severity of the insult as well as the host response, early intervention and development of secondary problems. When the condition is *recognized* early and treated aggressively 85% or more of these foals may survive as useful athletes.