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1. Introduction
The term neonatal maladjustment syndrome has been used to describe newborn foals that exhibit behavioral or neurologic abnormalities that are not related to infectious or toxic conditions, congenital or developmental abnormalities, or metabolic disorders. These foals have previously been classified as barkers, wanderers, dummies, or convulsants. The syndrome has been divided into four stages, which are preconvulsant, coma, semicoma, and wanderer. Numerous theories are given as the cause of the syndrome [1]. These include central nervous system (CNS) trauma and hemorrhage, and CNS anoxia. It seems that the majority of neonates exhibiting CNS signs within the first few days of life have suffered a lack of cerebral oxygen delivery resulting from either a lack of blood flow (ischemia) or decreased arterial oxygen tension (hypoxemia). Therefore, the descriptive term hypoxic ischemic encephalopathy (HIE), which has been adapted from human medicine, will be used in the remainder of this discussion.

2. Etiology and Pathogenesis
Intra-cranial hemorrhage caused by increased CNS pressure during birth or trauma has been proposed as a cause of CNS disease in the neonate. Vascular pressure changes and hemorrhage also may occur as a result of asphyxia. Many newborn foals with CNS disturbances have a history suggestive of decreased oxygen delivery during the perinatal period. This history, coupled with histopathologic findings similar to those described in other species with experimentally induced asphyxia, suggests that hypoxia and ischemia are important components of this syndrome in foals [2].

Interference with blood flow and oxygen delivery before birth can result from placental insufficiency or interference with uterine blood flow. A wide variety of conditions can result in interference with blood flow and oxygen delivery during parturition, such as obstruction of umbilical blood flow, premature placental separation, decreased uterine blood flow, and prolonged parturition (dystocia). During normal foaling, the fetus experiences a transient period of anoxia. The normal healthy foal is not affected by this period of oxygen deprivation; however, the compromised foal may not be able to compensate, and a cycle of events leading to exacerbation of the anoxia may result.

Events subsequent to birth can also lead to hypoxia and ischemia. Inadequate cardiac output can result in insufficient pulmonary or cerebral blood flow. The transition from fetal to adult circulation is critical to adequate oxygen delivery and can result in periods of inadequate delivery if there is a delay or if there is a reversion to fetal circulation. It is likely that responses to hypoxia at the cellular level are the same in all species. Mitochondrial swelling is followed by cytoplasmic vacuolization within minutes of the onset of hypoxia. Events subsequent to the intracellular "edema" include increased cerebral tissue pressure, focally decreased cerebral blood flow, generalized brain swelling, increased intracranial pressure, generalized decreased cerebral blood flow, and cerebral necrosis [2].

3. History
The history of a foal with HIE may include a report of gestational problems in the mare. Examples include vaginal discharge suggesting uterine or placental infection, colic or other medical problems during gestation, premature lactation, and prolonged or shortened gestational length. Some mares have histories of repeatedly delivering foals that develop signs of CNS disease. It is possible that these mares may have repeated problems during parturition or an inability to form an adequate placental unit. Premature placental separation is also commonly reported in the history of neonates with HIE [3]. Previous reports suggest that delivery of affected neonates may be fast and uncomplicated; however, more recent reports suggest that dystocia is
common in neonates with HIE. Delivery through emergency cesarean section is another risk factor for the development of hypoxic insults before or shortly after delivery.

A very important point to consider is that these neonates may be normal at birth and show no evidence of CNS disease for hours to days after delivery. Alternatively, these foals may exhibit evidence of violent CNS activity immediately or shortly after birth. This variation in onset of clinical signs is likely to be related to the degree of cell damage occurring as a result of the hypoxia-ischemia and possibly to the degree of edema that occurs as a result of cell death.

4. Clinical Signs

Clinical signs of HIE in neonatal foals are highly variable. The original descriptions of these foals as "barkers", "wanderers", or "convulsants" indicate the variation in clinical signs. Signs can be mild, such as a loss of affinity for the mare, an inappropriate suckle reflex, wandering, intermittent depression, and stargazing. Facial spasms, lip curling and chomping, or abnormal respiratory patterns may occur. The abnormal vocalizations (barking) are rarely identified. These foals may sleep deeply and may be difficult to arouse. These "mild" signs may be all that is seen, and the patient may recover without complication. On the other hand, signs may progress to more prominent and severe indications of CNS disease (Fig. 1, Fig. 2, Fig. 3). Foals may become totally unaware of the environment and appear to have blindness of central origin. Seizures may follow and are usually very sudden in onset, but are often preceded by one or more of the earlier mentioned signs. One of the more frequent premonitory signs of seizure is a "stretching" activity that actually may be a mild seizure. While lying down, the foal extends the front legs outward and lifts the head before again relaxing into a sternal sleeping position. Seizures can be of short duration with no subsequent evidence of obvious CNS disease. In more severe cases, seizures are severe and generalized with tonic-clonic convulsions, opisthotonus, and extensor rigidity. Some patients may paddle violently. If seizures are repetitive or continuous, foals are generally stuporous or comatose in the interictal period. Not all HIE patients develop seizures before progressing into a state of stupor.

The onset of clinical signs is extremely variable, and many foals may appear completely normal for hours to days. The onset of seizures has been reported to be as late as 4 - 5 days after birth [3]. Neonates also can be seen with CNS signs immediately after birth. The duration of clinical signs can also vary. These signs can be very brief, with single or no seizures to persistent stupor for several days. Usually foals recover in the reverse order in which the CNS signs developed, that is, stupor to awareness of the environment, standing, walking, and suckling. Typically, when foals recover from prolonged CNS derangement, relapses do not occur; however, recurrence of seizures subsequent to prolonged stupor has been seen.

5. Diagnosis

The diagnosis of the disease is based on typical clinical signs, historical information, and elimination of other possible causes of CNS disease in the newborn foal. As mentioned, the history often includes such factors as prepartum problems in the mare, problems during delivery, placental separation, and delivery using emergency cesarean section. When parturition includes any of these factors, close observation should ensue with special attention for early or mild evidence of CNS disease. The signs of CNS disease are not pathognomonic for HIE. Conditions that may also result in seizures include hyponatremia, hypocalcemia, hypoglycemia, hypomagnesemia, metabolic acidosis, generalized sepsis, parasite migration, Tyzzer's disease, viral encephalitis, drug-induced toxicities, hydrencephaly, liver failure, idiopathic epilepsy, and heat stroke. These conditions must be considered in the differential diagnosis but rarely cause seizures in the newborn foal. Those conditions that more
frequently cause CNS derangement in the neonate are cerebral contusion or hemorrhage possibly related to episodes of anoxia, hydrocephalus, and bacterial meningitis. The differentiation of the foal with hydrocephalus from one with HIE can be difficult. CNS abnormalities are not always present at birth in either case. The seizures in foals with hydrocephalus can be very severe, violent, and difficult to control. Foals with meningitis may have fevers. The CNS signs may first appear as periods of agitation with pawing, grinding of teeth, or sweating. The CNS signs in foals with meningitis may appear more like those in the adult horse with encephalopathy. These may include continuous and persistent wandering and circling, maniacal behavior, and head pressing. Results of laboratory data of the equine neonate with HIE are neither specific nor diagnostic; however, an elevated creatinine and elevated muscle enzyme levels are not uncommonly present in foals with HIE. The elevation in creatinine that is seen at birth has been suggested to be related to placental insufficiency, which may be related to a lack of adequate oxygen delivery in utero. The elevation in the muscle enzymes creatine kinase and aspartate aminotransferase may correlate with muscle hypoxia ischemia or trauma at birth. The leukogram in a foal with meningitis may suggest infection; however, it is not diagnostic. Clinical chemistry levels can be useful in excluding some of the less likely causes in CNS disease, such as metabolic or hepatic disease. Cerebrospinal fluid analysis is not diagnostic in the foal with HIE or hydrocephalus; however, increased cerebrospinal fluid cell counts can be diagnostic of meningitis. Radiographs of the skull may be useful in cases of severe trauma. Computerized axial tomography or magnetic resonance imaging can be used to diagnose hydrocephalus and is used in human medicine to differentiate hemorrhage from edema.

6. Treatment
The treatment of HIE is symptomatic. Supportive and nursing care are critical to the outcome of the case. The treatment of seizures varies depending on their severity. A seizure that is mild and brief may not need to be controlled; however, if seizures are recurrent or severe, treatment becomes necessary. The control of seizure activity can prevent trauma, reduce the energy consumption of seizures, and allow for better nursing care. A variety of convulsants can be used. Diazepam is the drug of choice for the immediate short-term suppression of seizures; 5 mg can be administered IV to the 50 kg foal (0.1 mg/kg). If this is not effective, repeated doses can be given. Diazepam is safe and fast acting, but its duration of action is short. If seizures persist, subsequent to the use of diazepam, alternative choices of drugs include phenobarbital, phenytoin, or sodium pentobarbital to effect. Phenobarbital can provide prolonged seizure control and is safe if given slowly and used to effect. The dosage is 10 - 20 mg/kg as a loading dose (10 mg/kg is often sufficient), diluted in saline and given over a 20- to 30-min period. Administration should stop if desired effects are achieved before the full dose is administered. Phenobarbital can be repeated as needed. Once seizures are controlled, oral administration (12 mg/kg, q 12 h) can be used for maintenance. Phenytoin, given initially at 5 - 10 mg/kg IV and subsequently at 1 - 5 mg/kg IV, IM, or PO every 2 - 4 h, may also be used. Disadvantages are the frequency of administration and cost. Intravenous sodium pentobarbital is an alternative choice that can be used. Approximately 2 - 4 mg/kg may be used in foals with uncontrollable seizures. Marked sedation or anesthesia may occur at higher or more frequent doses. Broad-spectrum antimicrobial therapy should be considered for the prevention of secondary infection in the compromised patient. Nutritional therapy is of utmost importance and varies with the severity of the condition. If the foal can stand but not suckle, an in-dwelling nasogastric tube may be used to provide adequate caloric support. The foal requires a minimum of 10% of its body weight in milk over a 24-h period. Feeding every 1 - 2 h is preferred. If the patient is recumbent but is able to maintain sternal recumbency, cautious enteral feeding is still possible, but care must be taken not to overfeed the recumbent foal. Enteral feeding must be provided sparingly in the stuporous foal. In these cases, caloric supplementation should be provided with continuous IV dextrose administration or more complete parenteral nutrition [4]. Intravenous fluids should be used judiciously in foals with HIE, because overhydration may worsen cerebral edema. It is wise to restrict fluid administration unless a secondary complication requires additional fluid therapy. When determining maintenance fluid requirements (4 ml/kg/h), oral fluid intake must be taken into account. A foal that is receiving 10% of its body weight in milk may not need additional IV fluids. Medications to reduce cerebral edema may be helpful. Intravenous dimethyl sulfoxide or mannitol can be useful in the acute stages of cerebral edema. Dimethyl sulfoxide (0.5 - 1.0 g/kg as a 10% solution IV) also has been recommended [5]. Hypertonic solutions such as mannitol should be used only if it can be definitively shown that cerebral hemorrhage is not present. In the presence of cerebral hemorrhage, hypertonic solutions can exacerbate edema. The use of corticosteroids is controversial because they can result in immune system suppression and can increase cerebral blood flow, which may worsen cerebral edema.

7. Prognosis
The prognosis for survival is dependent on the severity of the initial insult and progression of edema and cellular damage. Overwhelming hypoxia can result in a rapid onset of respiratory arrest. If cerebral damage results in fixed, dilated, and non-responsive pupils, the prognosis is grave. The CNS signs in many affected foals may not progress beyond a minimal loss of
recognition of the environment, with gradual recovery over a 1- to 2-day period. The prognosis for foals that have seizures is worse than for those that do not; however, if seizures can be controlled, adequate nursing care can be provided, and secondary complications can be avoided, the prognosis for these foals is good. Persistence of residual neurologic signs is unusual. When recovery does occur, there does not seem to be a long-term effect on growth or development.

References


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