Neonatal maladjustment syndrome in foals

Neonatal maladjustment syndrome is one of the most common neonatal foal diseases. It affects foals in the first 48 hours of life and causes a variety of clinical signs including loss of affinity for the mare, poor suck reflex and seizures. Many foals recover fully with supportive care. This article discusses the aetiology, clinical signs and treatment of the condition.

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Neonatal maladjustment syndrome is one of the most common neonatal foal diseases. This article discusses the aetiology, clinical signs and treatment of the condition.

Aetiology

Historically, the syndrome has been attributed to hypoxic–ischaemic injury at foaling and the condition is seen in foals that have experienced a prolonged delivery as a result of dystocia or premature placental separation. In these foals, hypoxia initiates a complex cascade of events that ultimately leads to primary and secondary cell death. The organs most commonly affected by hypoxia include the brain, kidneys and intestinal tract. Foals that have experienced significant hypoxia tend to show severe clinical signs and generally have a poorer prognosis for survival. Postmortem examination of these foals reveals evidence of hypoxic tissue injury and neuronal cell death (Rossdale and Leadon 1975; Aleman et al, 2019). This mirrors the situation in human medicine in which infants that have experienced significant birth hypoxia often have an increased mortality rate and are likely to suffer from long-term neurological dysfunction (Yildiz et al, 2017).

However, neonatal maladjustment syndrome occurs in many foals without a history of hypoxia and should be considered a syndrome with multiple possible causes. A large subset of foals with neonatal maladjustment syndrome experiences abnormalities in the birth transition process (Diesch and Mellor, 2013). In a normal foal, progestagen concentrations are high at birth because they are produced by the placenta and fetal hypothalamic–pituitary–adrenal (HPA) axis. These compounds have a role in fetal quiescence (Mellor and Lentle, 2015). In a healthy foal the final maturation of the HPA axis converts progestagens to cortisol and other compounds. Cortisol is essential for the final maturation of many body systems. This increased HPA activity and loss of placental supply of progestagens means that progestagen levels are negligible by 48 hours after birth (Houghton et al, 1991).

In foals with neonatal maladjustment syndrome, progestagen concentrations remain high after foaling or begin to fall and then rise again sharply (Aleman et al, 2013). Why this failure in the birth transition process occurs is not completely understood. Factors that are likely to have a role include systemic inflammation, mild or chronic hypoxia, abnormal delivery and placental disease (Toribio, 2019). In some foals that develop neonatal maladjustment syndrome it has been observed that foaling is unusually rapid and it is possible that the physical pressure of the birth canal is an important stimulus for these normal maturation pathways. In foals that recover from neonatal maladjustment syndrome, progestagen concentrations decrease in line with their recovery.

Abnormal progestagen concentrations may contribute to the clinical signs of neonatal maladjustment syndrome. Many progestagen compounds are able to cross the blood–brain barrier and have neuroactive effects. Experimentally, infusion of certain progestagen compounds can cause sedation and reduced consciousness in healthy foals (Madigan et al, 2012).

Clinical presentation

Clinical signs of neonatal maladjustment syndrome occur from birth until 72 hours of age. Neurological signs are often the most common (*Figure 1*). These can range from a foal that appears slightly 'slow' to a foal with marked obtundation or uncontrollable seizures. Common signs include loss of suck reflex, lack of affinity for the mare, altered mentation, abnormal head carriage, hyper-responsiveness, increased muscle tone and seizures.

Multiple body systems are usually involved. Gastrointestinal signs range from dysmotility to severe ileus. Reduced faecal output and meconium retention are common. Many foals have decreased gastrointestinal motility and are unable to tolerate large volumes of milk. Some of these foals will develop abdominal distension, nasogastric reflux and colic.

Central control of respiration can be altered and many foals develop an abnormal pattern of breathing. Apnoea or prolonged

periods of breath holding occur in some foals while others develop persistent tachypnoea. In foals that become recumbent or develop secondary sepsis, secondary respiratory problems with atelectasis and pneumonia can occur. Pharyngeal dysfunction can also occur with poor coordination of the upper respiratory tract musculature. This can cause nasal return of milk, increased upper respiratory tract noise and milk aspiration. Milk aspiration can lead to bacterial pneumonia.

Renal dysfunction often leads to reduced renal concentrating ability and can manifest as oliguria or anuria. Renal dysfunction can lead to fluid and sodium retention followed by tissue oedema in foals given intravenous fluid therapy.

All other body systems can also be affected and many foals will display abnormalities in the cardiovascular, endocrine and metabolic systems.

Diagnosis

Diagnosis relies heavily on clinical signs and the exclusion (or inclusion) of other conditions. Careful physical examination and an accurate history usually give a good indication as to the likelihood of the disease. Haematological and biochemical analysis and measurement of blood pressure, blood gases and blood lactate levels will help determine the degree of involvement of different organs and the severity of the disease. Progestagen concentrations can also be measured but are not specific for a diagnosis of neonatal maladjustment syndrome (Dembek et al, 2017). Ultrasound can be useful to assess the extent of gastrointestinal involvement.

Treatment

The majority of foals with neonatal maladjustment syndrome will survive if given early and appropriate supportive care (Lyle-Dugas et al, 2017). Many foals with mild neonatal maladjustment syndrome can be managed successfully on the farm (Aleman et al, 2017). Once foals have been allowed to develop secondary complications, such as sepsis, the survival rate decreases. Early supportive care is the key to treatment. Foals that have experienced a significant hypoxic injury are much more difficult to treat and can require the highest level of intensive care (*Figure 2*).

The main aims of treatment are to maintain hydration, provide nutrition, prevent sepsis, encourage maternal bonding and control seizures or other neurological signs.

It is important to maintain adequate tissue perfusion, which frequently involves the use of intravenous fluid therapy. Cautious replacement fluid therapy may be necessary to restore circulating volume in foals that are hypovolaemic. This can be provided with small boluses of isotonic crystalloids (10–20 ml/kg over 20–30 minutes). However, these fluids must be used carefully to prevent fluid and sodium overload. Many foals will then benefit from maintenance intravenous fluid therapy with 5% dextrose or another low sodium maintenance fluid (usually 3–5 ml/kg/hr). Inotropes and pressors may be necessary in more severe cases to maintain blood pressure and tissue perfusion. Foals which require this level of supportive care are generally better managed in a hospital environment.

Nutritional support is essential. The simplest way to provide this is via enteral feeding. Some foals may just need some assistance

Figure 1. These foals are both demonstrating common neurological clinical signs: abnormal tongue position and poor suck reflex (a) and pronounced head tilt (b).

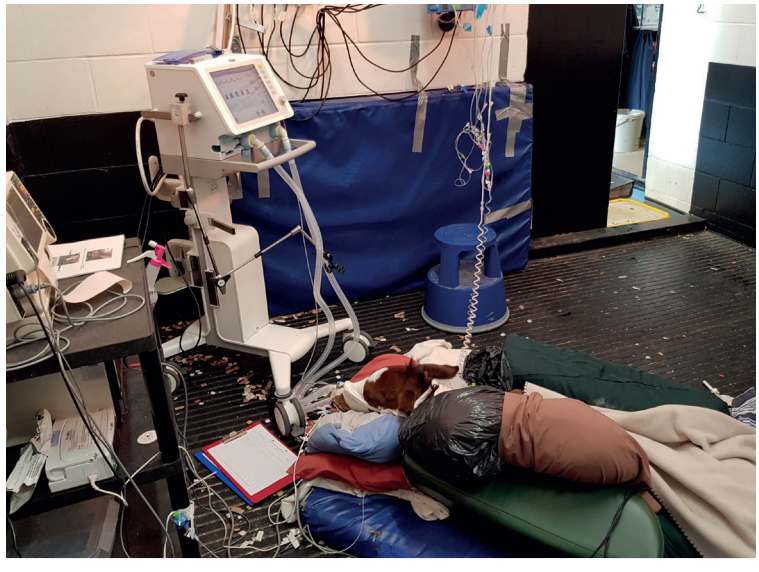

Figure 2. Foals with advanced disease or secondary complications such as sepsis often require a high level of intensive care. This foal is receiving high level supportive care with positive pressure ventilation and advanced fluid therapy.

to stand and latch on. However, many foals have a poor suck reflex and consequently find it difficult to nurse from the mare. Bottle feeding is usually not advisable as milk aspiration is likely. The use of a small indwelling nasogastric tube is often preferable to allow small, frequent feeds (*Figure 3*). These tubes can be simply and safely placed in the farm environment and the tube position can be confirmed by palpation of the tube in the proximal oesophagus just caudal to the larynx. Enteral feeding should be monitored very closely as not all foals will tolerate large volumes of milk. A good initial target that will provide maintenance fluid and energy requirements is 10% of bodyweight per 24 hours; a 50 kg foal would have a daily milk requirement of 5 litres. Foals with more severe

disease will not tolerate enteral feeding and parenteral nutrition might be required. There are many benefits to providing nutrition via the enteral route and small trophic feeds should be provided in foals that are unable to tolerate significant milk feeding.

Recumbent or severely affected foals may benefit from respiratory support. This is generally possible using humidified intranasal oxygen at 2–15 litres/minute. Sternal positioning and encouraging mobility can also significantly improve lung function. Arterial blood gas analysis can be useful to monitor respiratory function. Preventing hyperoxia is important because it can increase oxidative injury. Foals with abnormal central control of respiration can also develop excessive hypercapnia. In these foals the use of respiratory stimulants can reduce hypoventilation. Doxapram hydrochloride can be given as a continuous infusion but should be monitored very carefully. Caffeine can be given orally and with less monitoring but is generally less effective (Giguère et al, 2008).

Figure 3. A small bore indwelling nasogastric tube is often the best way to provide nutrition.

Figure 4. The 'squeeze' procedure can improve clinical signs in some foals.

KEY POINTS

- High standards of nursing care and hygiene are required.
- The foal with neonatal maladjustment syndrome should be bedded on soft bedding close to the mare.
- Regular turning and encouragement to stand are important and the foal's limbs and eyes should be protected from trauma.
- Eyes should be monitored for ulceration and entropion and corneal lubricants can be useful.
- Care should be taken to ensure that the skin remains dry.

Diazepam (0.1–0.2 mg/kg intravenously) can be used for short-term control of seizures. However, the drug accumulates in tissue and is not suitable for longer term use. Midazolam by continuous rate infusion is an excellent choice when more prolonged treatment (from 6 to 72 hours or more) is required. This drug has the advantage that the rate can be adjusted relatively easily and the medication can be discontinued without a prolonged effect. Phenobarbitone (2–10 mg/kg by slow intravenous infusion every 8 hours reduces central nervous system excitability and can be used for control of frequent, more severe seizures. A small single dose (2–4mg/kg) can provide adequate control in some foals, or dosing can be repeated as necessary (maximum 3 doses per 24 hour window). The drug can cause profound respiratory suppression so should be used at the lowest effective dose rate.

Many other treatments have been proposed for the treatment of neonatal maladjustment syndrome. There is very little evidence to support their use (Toribio, 2019). The use of antioxidants such as vitamin E, C and thiamine may help reduce oxidative damage. Magnesium sulphate has been suggested to prevent cellular death. There are no studies evaluating its use in foals and the studies from human medicine are conflicting. Dimethyl sulfoxide (DMSO), mannitol and dexamethasone have all been suggested to reduce cerebral oedema. There are no studies on their effects in horses, but both mannitol and DMSO can create problems with high osmalility and they are probably best avoided (Langdon-Fielding and Magdesian, 2014).

Control or prevention of sepsis is absolutely critical. Foals should be checked for failure of passive transfer and plasma administered if necessary. Broad-spectrum antimicrobial therapy should be considered in any foal that is judged to be at high risk for sepsis or shows any clinical signs of infection. A full discussion about antimicrobial use is beyond the scope of this article, but an excellent review is provided by Magdesian (2017).

There is a great deal of interest in ways to reduce progestagen concentrations. However, it is still not known whether this is an appropriate way to try and accelerate recovery in these foals or whether there may be a protective benefit from the high levels of these compounds (Toribio, 2019). Anecdotally, 5 alpha reductase inhibitors such as dutasteride and finastaride have been trialled but there is no evidence to support their use.

A technique called 'squeeze-induced somnolence' or the 'foal squeeze' has been developed over the past few years to try to recreate the physical pressure of the birth process (Aleman et al, 2017) (*Figure 4*). The idea behind this technique is that the physical pressure of foaling is an important trigger in reducing progestagen concentrations. In some foals this leads to a dramatic and rapid improvement in their clinical signs. This procedure can be easily carried out using a soft cotton rope. Further instructions can be found at http://www.equineneonatalmanual.com/foalsqueezing.

Prognosis

The prognosis for foals with neonatal maladjustment syndrome is usually very good with appropriate supportive care. Reported survival rates range widely but can be as high as 80–90% (Lyle-Dugas et al, 2017). The prognosis for foals that experience significant severe hypoxic injury is generally poorer. Signs of uncontrollable seizures, anuric renal failure and severe cardiovascular dysfunction are generally associated with a poor prognosis. The long-term outlook for full athletic function is generally excellent for foals that survive (Chidlow et al, 2019). EQ

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