Clinical Commentary

Metabolic disorders in foals

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Introduction

The metabolic processes are those that are used to extract or convert the substances required for cellular activity and growth from feedstuffs. A very large number of metabolic disorders have been described in man, which can be congenital (inborn errors of metabolism) or acquired. In contrast, very few metabolic disorders have been described in the horse and particularly the foal. In this issue of Equine Veterinary Education, Unt et al. (2012) describe in detail a case of the metabolic disorder intestinal hyperammonaemia in a 7-week-old foal. This case was previously described (as Case 28) in a series of 36 cases of hyperammonaemia, which included 7 foals that were aged <2 months and three 4–9-month-old foals (Dunkel et al. 2011).

This commentary will give current knowledge on metabolic diseases in the foal.

Inborn errors of metabolism

Hyperammonaemia

Hyperammonaemia has been described as an inborn error of metabolism in Morgan foals (McConnico et al. 1997). These foals may have had an analogous condition to the inherited condition described in man, hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome. In man, HHH syndrome is associated with a defect in the transport of ornithine across the inner mitochondrial membrane, preventing the production of citrulline from carbamoyl phosphate and ornithine by the action of the enzyme ornithine transcarbamoylase in the urea cycle. Carbamoyl phosphate is produced from ammonium, bicarbonate and ATP, and the failure of ornithine to cross the mitochondrial membrane results in the build-up of ammonium (Testai and Gorelick 2010).

The 2 affected foals showed depression, dementia, anorexia, aimless wandering and circling in both directions. One foal also showed yawning behaviour. Treatment consisting of supportive care followed by a low protein diet and lactulose was attempted in one of the 2 foals. Both foals were subjected to euthanasia (McConnico et al. 1997). In man, treatment consists of a low protein diet supplemented with essential amino acids. In addition, patients are treated with arginine hydrochloride, sodium benzoate and sodium phenylacetate infusion, which are intermediaries of alternative nitrogen excretion pathways. Peritoneal dialysis and haemodialysis are occasionally used in refractory cases (Testai and Gorelick 2010).

Polysaccharide storage myopathy

Polysaccharide storage myopathy (PSSM) is a genetic condition that can manifest in weanlings as persistent increases in creatine kinase and muscle atrophy (De La Corte et al. 2002). In Quarter Horses, PSSM is a result of a gain of function mutation in the gene encoding skeletal muscle glycogen synthase (McCue et al. 2008). PSSM results in excess glycogen as well as abnormal amylase resistant polysaccharide accumulating in types 2A and 2B skeletal muscle fibres (De La Corte et al. 1999).

Polysaccharide storage myopathy is present in approximately 36% of draught horses (Firshman et al. 2005) and 10% of Quarter Horses (McCue and Valberg 2007). Although clinical signs can be apparent in weanlings, signs are not usually apparent until horses are put into exercise (De La Corte et al. 2002). Clinical signs vary from muscle atrophy and progressive weakness in draught horse breeds to muscle soreness and gait abnormalities in Warmblood breeds, and acute exertional rhabdomyolysis in Quarter Horses (McCue et al. 2008). PSSM has also been reported in many other breeds (Stanley and Piercy 2007). Diagnosis of PSSM is by muscle biopsy. Treatment during acute episodes is symptomatic including analgesics, sedatives or anxiolytics and fluid therapy (Valentine 2003). Long-term treatment of PSSM involves dietary modification to increase the amount of energy from fat to at least 20% of the total energy in the diet (Valentine 2003).

Glycogen branching enzyme deficiency

Glycogen storage disease type IV was diagnosed in 7 related Quarter Horse foals, that all died by age 7 weeks...
Clinical signs appear to have been somewhat varied between foals, although they all showed weakness. Three of the foals showed flexural deformity of all 4 limbs. Post mortem lesions of periodic acid Schiff’s (PAS)-positive globular or crystalline intracellular inclusions were found in skeletal and cardiac muscle and in the liver in affected foals (Valberg et al. 2001).

In man, glycogen storage disease type IV is a very heterogeneous disease, partly because of the variety of tissues that can be affected (Ozen 2007). The classic form is a liver disease, resulting in cirrhosis and liver failure at age 3–5 years (Andersen 1956). In the fetal form of the disease, the affected baby has severe hypotonia and arthrogryposis of lower limbs in addition to hydrops fetalis (Alegria et al. 1999). There is also a milder juvenile form of human glycogen storage disease type IV that manifests as a myopathy affecting the cardiac and skeletal muscles (Reusche et al. 1992).

In Quarter Horses, the genetic lesion has been identified as a single base nonsense mutation in the glycogen branching enzyme, encoded by the GBE1 gene (Ward et al. 2006; Tryon et al. 2009).

Calcium metabolism

Primary hypoparathyroidism has been described in a 3-month-old foal (Durie et al. 2010). The foal presented with sweating, stiffness, muscle twitching and synchronous diaphragmatic flutter. The foal was treated with i.v. calcium and then oral calcium and vitamin D3 contained within an i.m. preparation of vitamins A, D3 and E. At age 7 months, the foal had a normal plasma calcium concentration and at age one year was considered to be healthy (Durie et al. 2010).

A syndrome of idiopathic hypocalcaemia, unresponsive to oral calcium and synthetic 1,25-dihydroxycholecalciferol treatment, has been described in 5 foals aged 4 days to 5 weeks. Parathyroid hormone was measured in 3 of the foals, and was normal in one foal, increased in the second and undetectable in the third (Beyer et al. 2004). Since the cause of the hypocalcaemia was not identified, it is not certain that these foals had an inborn error of metabolism. In man, both genetic (Greig et al. 1996; Pearce et al. 1996) and acquired (Salle et al. 1990) forms of neonatal hypocalcaemia have been described.

Diabetes mellitus type 1

In man, both transient and permanent neonatal diabetes mellitus have been associated with chromosomal mutations (Flanagan et al. 2007; Ioannou et al. 2011). A transient diabetes mellitus was reported in a 3-day-old Thoroughbred foal with diarrhoea associated with a presumed coronavirus infection (Navas de Solis and Foreman 2010). Although derangements in glucose metabolism and insulin production and sensitivity have been reported as a feature of sepsis in neonatal foals (Hollis et al. 2008; Barsnick et al. 2011), the requirement for insulin was particularly prolonged in this foal for 31 days (Navas de Solis and Foreman 2010) compared to the typical period of 2–4 days in a foal with sepsis (K.T.T. Corley, unpublished observations 2011). It is therefore possible that this foal had a condition analogous to the transient neonatal diabetes mellitus reported in man (Flanagan et al. 2007).

Acquired metabolic disease

Hyperammonaemia of intestinal origin

In this issue, Unt et al. (2012) present a case of intestinal hyperammonaemia in a foal. This condition has recently been reviewed in this journal (Dunkel 2010).

Two sources of ammonium from the intestine have been described (Dunkel 2010). The first is from the bacterial breakdown of urea, amino acids and proteins in the large intestine. Clostridial species have been implicated in 2 cases in mature horses (Desrochers et al. 2003; Stickle et al. 2006), but in most cases the causative bacteria are not identified. The faecal and therefore presumably intestinal bacterial flora of young foals is different from that of mature horses for the first 4 weeks of life (Kuhl et al. 2011). Staphylococci and Enterococci, 2 of the bacteria that have been implicated in human ammonium production (Burne and Chen 2000), are not present in large numbers in the first few days of life (Kuhl et al. 2011). Therefore the second proposed mechanism of intestinal ammonium production, deamination of glutamine by phosphate-activated glutaminase located in villus enterocytes of the small intestine (Romero-Gomez et al. 2009; Dunkel 2010), could be responsible for intestinal ammonia production in foals. That said, the case reported by Unt et al. (2012) and 3 additional foals aged <1 month reported by Dunkel et al. (2011) had a primary diagnosis of colitis or enterocolitis, suggesting that the large intestinal flora may have changed considerably. The further 3 young foals reported by Dunkel et al. (2011) had a primary diagnosis of meconium impaction.

In the recent case-series, 5 out of the 7 foals (71.4%) survived to hospital discharge compared to 9 out of 26 mature horses (34.6%). The 2 foals that died had a diagnosis of colitis or enterocolitis (Dunkel et al. 2011).

Sepsis

Sepsis has been reported to be associated with several metabolic disorders in foals including derangements of glucose regulation (Hollis et al. 2008; Barsnick et al. 2011), calcium regulation (Hurcombe et al. 2009), thyroid production (Breuhaus and LaFevers 2005; Himler et al. 2010) and of the lactate cycle (Corley et al. 2005;
Wotman et al. 2009). Whereas the mechanisms of these derangements have not been fully elucidated in the foal, it is assumed that they closely mirror those seen in man and experimental animal models of sepsis (Fink 1997; Mizock 2000). Treatment of these derangements consists of supporting the metabolism whilst removing the primary source of sepsis either by surgery or antimicrobial treatment.

**Perinatal asphyxia syndrome**

Hypercalcaemia has been reported in foals with perinatal asphyxia syndrome in the absence of renal disease, hyperparathyroidism or excessive calcium administration (Toribio 2011). The cause of the hypercalcaemia is unknown. Foals with severe perinatal asphyxia syndrome show many similar symptoms to those with sepsis (Corley and Furr 2003; Hollis et al. 2008), presumably because both conditions result in activation of the systemic inflammatory response syndrome (Corley et al. 2000, 2005). Treatment consists of supporting the metabolism during the period of crisis and allowing the hypoxic-ischaemic lesions to heal. The efficacy of specific treatments aimed at hastening tissue recovery from hypoxic-ischaemic insult remains unproven.

**Conclusion**

Metabolic disorders are relatively rare in foals. The most common are those seen secondary to major systemic disease such as sepsis and perinatal asphyxia syndrome. Inborn errors of metabolism have been very rarely reported in foals. Some of these conditions, such as PSSM, are rare and manifest clinically until the animals are mature. Other inborn conditions, such as hyperammonaemia, have been reported in a very small number of foals.

Intestinal hyperammonaemia is an acquired condition that had, until 2011, only been reported in mature horses. The report by Unt et al. (2012) in this issue, together with the case series from Dunkel et al. (2011) highlights that the condition can indeed occur in foals and that perhaps we should be more vigilant for it.

**Author’s declaration of interests**

No conflicts of interest have been declared.

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