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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

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(Valberg *et al*. 2001). 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 (subcutaneous oedema, pleural effusion and ascites) (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*. 2004). This gene is carried by approximately 2–5% of Quarter Horses and American Paint Horses and was not found in Thoroughbreds (Wagner *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*. 1997). 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 present at a relatively high incidence in certain breeds but rarely 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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