EQUINE VETERINARY EDUCATION
Equine vet. Educ. (2009) **21** (8) 415-419
doi: 10.2746/095777309X453119

Clinical Commentary

Equine proliferative enteropathy caused by *Lawsonia intracellularis*

N. Pusterla* and C. Gebhart†

Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California 95616; and †Department of Veterinary and Biomedical Sciences, University of Minnesota, College of Veterinary Medicine, St Paul, Minnesota 55108, USA.

Keywords: horse; *Lawsonia intracellularis*; proliferative enteropathy; clinical signs; diagnosis; treatment

Summary

Equine proliferative enteropathy (EPE) is a disease of foals caused by the obligate intracellular organism *Lawsonia intracellularis*. This emerging disease affects mainly weanling foals and causes fever, lethargy, peripheral oedema, diarrhoea, colic and weight loss. The diagnosis of EPE may be challenging and relies on the presence of hypoproteinaemia, thickening of segments of the small intestinal wall observed on abdominal ultrasonography, positive serology and molecular detection of *L. intracellularis* in faeces. Although the clinical entity, diagnostic work-up and treatment of EPE are well established and described, the epidemiology for this disease has remained largely unaddressed. This article reviews the aetiology, epidemiology, clinical signs, diagnosis, treatment and prevention of EPE.

Introduction

The accompanying report by Allen *et al.* (2009) describes an unusual case of *Lawsonia intracellularis* proliferative enteropathy (PE) with concurrent lymphocytic, plasmacytic enteritis. Although the correlation between the 2 enteropathies has not been established, this report illustrates an increasing awareness of a recently described disorder in foals.

Lawsonia intracellularis is the aetiological agent of the recently recognised and emerging intestinal disease in horses, called equine PE (EPE) (Lavoie *et al.* 2000). *L. intracellularis* is an obligate intracellular, curved, Gram-negative bacterium that resides freely within the apical cytoplasm of infected intestinal enterocytes. It causes proliferation of the affected enterocytes, resulting in a thickened small and sometimes large intestine. *L. intracellularis* can only be grown *in vitro* in cell culture and requires a specific atmosphere for growth. Besides horses, *L. intracellularis* infects many species of domestic and wild animals, including pigs, hamsters, rabbits, fox, deer, ferrets, ostriches and nonhuman primates. EPE was first reported in horses in 1982 by Duhamel and Wheeldon (1982). Since 1996, many more reports of sporadic cases (Williams *et al.* 1996; Frank *et al.* 1998; Brees *et al.* 1999; Schumacher *et al.* 2000; Bihr 2003; McClintock and Collins 2004; Deprez *et al.* 2005; Dauvillier *et al.* 2006; Sampieri *et al.* 2006; Wuersch *et al.* 2006; Feary *et al.* 2007) and outbreaks on breeding farms (Lavoie *et al.* 2000; McGurrin *et al.* 2007; Frazer 2008; Merlo *et al.* 2009) have been described. In the last few years, reported cases of EPE have been increasing, primarily in post weaning foals and occasionally in adult horses. The disease has almost reached a worldwide distribution and has been reported in the USA, Canada, Europe, South Africa and Australia.

Molecular investigations of *L. intracellularis* isolates from PE lesions of a variety of animal species, including horses and hamsters, showed 98% homology of the 16S-rDNA gene to pig isolates (Cooper and Gebhart 1998). Moreover, phenotypic characterisation of outer membrane proteins and immunoblots of different *L. intracellularis* isolates using several antibodies and more sensitive molecular characterisations of the *L. intracellularis* genome demonstrated only minor differences among isolates. None of these differences appears to be antigenically relevant. A preliminary investigation into the epidemiological relationships between *L. intracellularis* isolates from pigs and horses suggests that they represent different strains and therefore may be species specific (Al-Ghamdi 2003).

Epidemiology

In piglets, large group size, weaning, transportation, diet change and mixing have been associated with clinical

*Author to whom correspondence should be addressed.

disease. Predisposing factors such as the stress of weaning and parasitism have been suggested in the development of PE in foals. The route of infection for weanling foals remains unknown, however, in comparison to other species, a faeco-oral route is suspected, via contaminated feed and/or water. In pigs, the incubation period is 2–3 weeks following exposure; however, this period has not been determined for horses. Because of the wide host range of PE, numerous potential reservoir hosts exist. *Lawsonia intracellularis* has recently been detected by PCR from the faeces of a variety of domestic and wild animals (Herbst *et al.* 2003; Tomanová *et al.* 2003; Pusterla *et al.* 2008a). Despite an ever-increasing range of host species, *L. intracellularis* is currently not to be considered a zoonotic disease. The role of clinically and subclinically infected horses in the transmission of *L. intracellularis* needs further investigation.

Epidemiological investigations on premises from which clinical cases have been identified have revealed that 10–65% of unaffected foals and adult horses test seropositive for *L. intracellularis* (Frazer 2008; Pusterla *et al.* 2008b, 2009a).

Clinical presentation

There are characteristic signalment, seasonality, clinical signs and blood work abnormalities associated with EPE. The disease is generally manifested in foals aged 2–8 months and in North America is often seen between August and January (Frazer 2008). Lethargy, anorexia, fever, peripheral oedema (ventrum, sheath, throatlatch and distal limbs; **Figs 1** and **2**), weight loss (**Fig 3**) colic and diarrhoea (**Fig 4**) are amongst the most common clinical findings in affected foals. Although diarrhoea is commonly seen in affected foals and can vary from 'cow pat' to watery, some affected foals may have normal faecal character. Foals with EPE may also have concurrent disorders such as respiratory tract infections, gastric ulcerations and intestinal parasitism. One must keep in mind that signs of EPE may resemble those of more common gastrointestinal disorders such as parasitism, bacterial infections (*Clostridium* spp., *Salmonella* spp., *Rhodococcus equi*), rotavirus, coronavirus, ulcerations, sand accumulation and intestinal obstruction. Similar to pigs, the disease is often subclinical in foals; however, it will remain to be determined if growth retardation or unthriftiness is associated with subclinical infection.

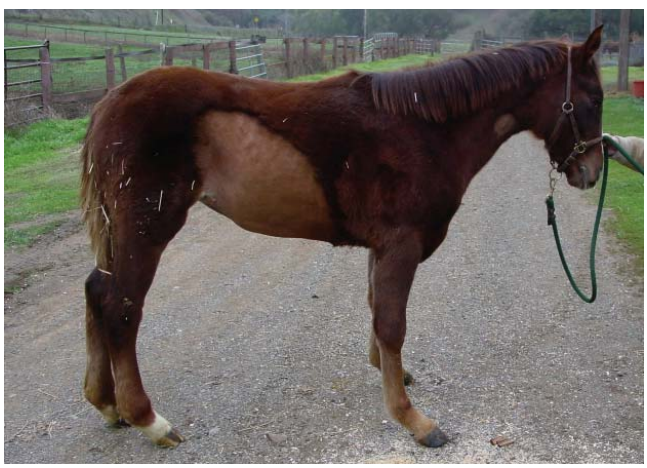

Fig 1: Ventral and distal limb oedema in a 7-month-old Thoroughbred filly with proliferative enteropathy.

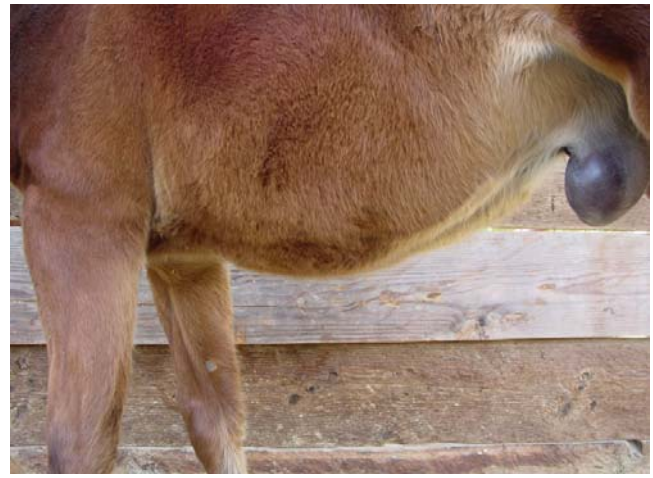

Fig 2: Ventral and sheath oedema in a 8-month-old Quarter Horse colt with proliferative enteropathy.

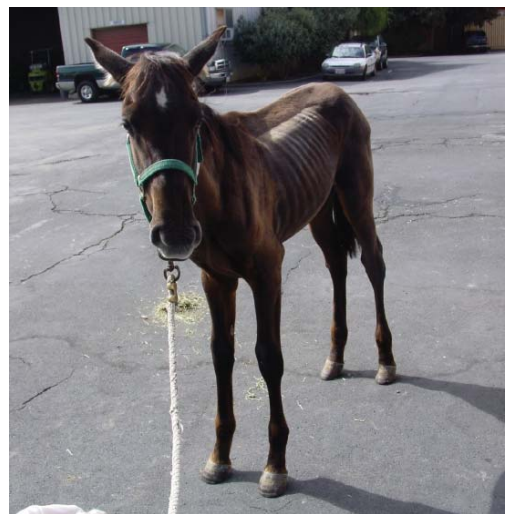

Fig 3: Severe weight loss in a 5-month-old Friesian colt with proliferative enteropathy.

Diagnostic evaluation

The *ante mortem* diagnosis of EPE may be challenging and relies on the presence of hypoproteinaemia, exclusion of common enteric diseases, thickening of segments of the small intestinal wall observed on abdominal ultrasonography, positive serology and molecular detection of *L. intracellularis* in faeces.

The most consistent laboratory finding is hypoproteinaemia due to hypoalbuminaemia. Total

Fig 4: Diarrhoea in a 8-month-old Thoroughbred colt with proliferative enteropathy.

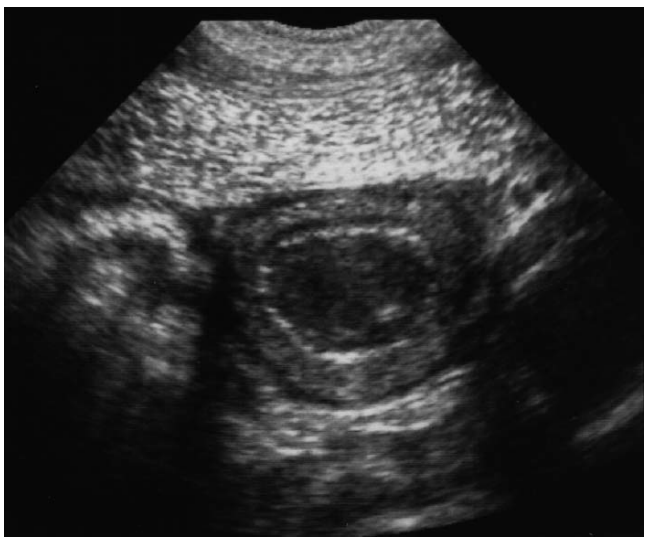

Fig 5: Ultrasound image showing thickened section of small intestinal wall in a 6-month-old Quarter Horse filly with proliferative enteropathy. The wall thickness measured 4.3 mm (normal wall thickness ≤3 mm).

protein concentration is generally less than 50 g/l and albumin is usually <20 g/l. In a recent case report by Frazer (2008), hypoalbuminaemia was the only consistent clinicopathological abnormality of 57 affected foals with albumin concentrations ranging from 9–33 g/l (normal reference range 31–41 g/l). Affected foals may also demonstrate nonspecific blood abnormalities such as anaemia or haemoconcentration, leucocytosis or neutropenia, hyperfibrinogenaemia, increased activity of muscle enzymes and electrolyte abnormalities (hypocalcaemia, hypochloraemia and hyponatraemia).

Abdominal ultrasonography, although not very sensitive, may show segments of thickened small intestine (**Fig 5**) and excessive abdominal fluid. In these cases, abdominocentesis will yield a noninflammatory transudate.

Culture of *L. intracellularis* from faeces is not practical due to its obligate intracellular nature. Several PCR assays have been developed for the detection of *L. intracellularis* in faeces. The sensitivity and specificity of the PCR technique in faecal samples has been evaluated for pigs and showed variable sensitivity and consistently high specificity (Guedes *et al.* 2002; Jacobson *et al.* 2004). Sensitivity is affected by sample quality and the presence of inhibitory factors in faeces. PCR appears to reliably demonstrate *L. intracellularis* in the faeces of clinically affected horses early in the course of the disease but often fails to detect the organism in the faeces of subclinically infected animals, animals with prolonged course of disease or foals treated with antimicrobials prior to faecal analysis.

Animals exposed to *L. intracellularis* develop serum IgG antibodies specific for the organism. Current methods used for serological diagnosis of PE employ *L. intracellularis* cultured in enterocytes or a preparation of *L. intracellularis* on slides as the antigen. Staining of bacteria is either by a fluorescent (indirect fluorescent antibody) or peroxidase-labelled (immunoperoxidase monolayer assay) secondary antibody. One must keep in mind that a positive serological result may represent exposure to infection rather than disease. Although no commercially available serological assay has yet been systemically evaluated for the equine species, serological assays have proven useful

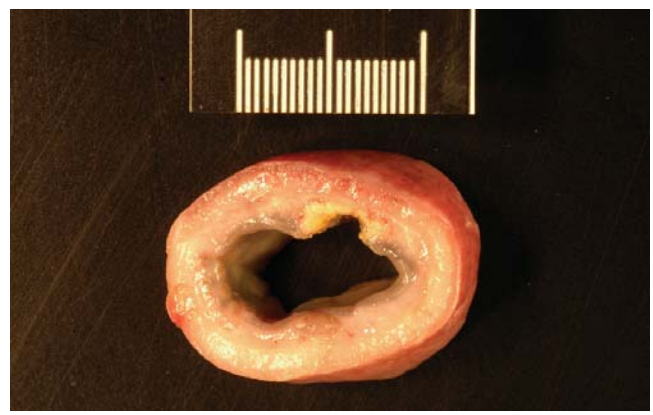

Fig 6: Cross-section of ileum of a 8-month-old Thoroughbred foal with proliferative enteropathy showing diffusely thickened intestinal wall.

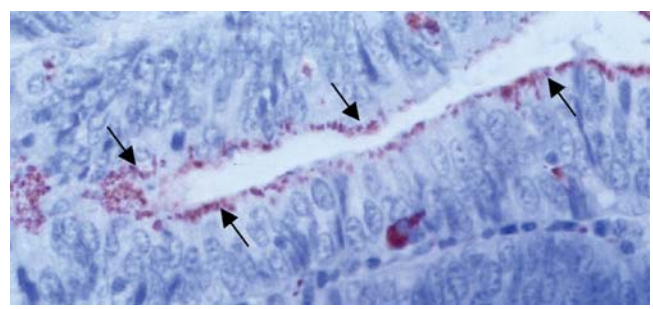

Fig 7: Immunohistochemical staining with* L. intracellularis*-specific antibody of ileal mucosa from a foal with proliferative enteropathy. Epithelial cells of hyperplastic crypts have aggregates of bacteria lining the apical cytoplasm (arrows).

for routine diagnosis of PE in horses, when combined with clinical signs and molecular detection of *L. intracellularis* in the faeces.

Lesions are most commonly seen in the ileum, near the ileo-caecal junction, and appear as a thickening of the mucosa (**Fig 6**). Gross lesions are not evident in all cases of EPE and may often be overlooked. Severe PE is diagnosed by the demonstration of hyperplasia of the crypt glands with an increased number of mitotic figures and absence of goblet cells in routine haematoxylin and eosin preparations; however, for visualisation of the bacteria in the cytoplasm of enterocytes, special stains are necessary. The histological lesions of PE are unique and inflammation is not normally a hallmark of the disease. Warthin-Starry silver stain allows the detection of the bacteria in histological sections, improving the diagnostic sensitivity, but the technique has limitations when applied to autolysed and necrotic samples. Immunohistochemistry procedures, using *post mortem* tissue or biopsy material, with an antibody specific for *L. intracellularis* have been used successfully to diagnosis EPE (**Fig 7**).

Treatment and prevention

It is important to treat affected animals early, before lesions become advanced resulting in marked weight loss and critically low serum protein values. Treatment of EPE in horses involves the use of antimicrobials such as macrolides alone or in combination with rifampin, chloramphenicol, oxytetracycline or doxycycline administered for 3 weeks. The choice of antimicrobial in the treatment of EPE should take into account the risk of inducing disturbance of the gastrointestinal flora and renal toxicity. This is especially a concern when treating older foals with severe hypoalbuminaemia. In addition, supportive care such as i.v. fluids, plasma transfusion, parenteral nutrition and anti-ulcer drugs are commonly used to treat affected foals. Concurrent medical conditions should also be addressed. Rapid clinical improvement following treatment is to be expected, although it may take weeks for the hypoproteinaemia to resolve. Spontaneous recovery of clinically affected foals has not been documented and treated foals usually survive the disease. Long-term sequelae have not been reported; however, clinically affected and successfully treated foals sell for an average of 68% less than the average price of unaffected foals by the same stallion (Frazer 2008).

Prevention strategies have been best described in pigs using in-feed antimicrobials and a commercially available *L. intracellularis* vaccine (Lawson and Gebhart 2000; Kroll *et al.* 2004; McOrist and Smits 2007). Recent work has shown that detectable humoral response can be measured in foals administered an avirulent live *L. intracellularis* vaccine (Pusterla *et al.* 2009b). However, the efficacy and protection conferred by this strategy needs to be further investigated via field efficacy trials and experimental challenge studies.

Conclusion

Equine proliferative enteropathy is an emerging disease in horses caused by *L. intracellularis*, an obligate intracellular bacterium. Increased awareness of this disease in the field and the availability of diagnostics for detecting the organism in horses have resulted in increased reports of the disease worldwide. The epidemiology and pathogenesis of *L. intracellularis* infection in horses are now being actively investigated.

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