PROLIFERATIVE ENTEROPATHY OF HORSES (A REVIEW ARTICLE)

Al-Ghamdi, G. M.

Department of Clinical Studies, College of Veterinary Medicine and Animal Resources, King Faisal University, Al-Ahsa 31982 Saudi Arabia

ABSTRACT

Proliferative enteropathy (PE) is a recently described disease of horses that is characterized by signs of elevated body temperature, weight loss, diarrhea and death. The disease is caused by Lawsonia intracellularis. Treatment may include flunixin meglumine, dexamethasone and prednisone to control inflammation. In addition antiulcer drugs such as cimetidine may be required. Finally, antibiotic therapy such as oral administration of combined erythromycin/rifampin, or chloramphenicool and oxytetracycline should be initiated.

PROLIFERATIVE ENTEROPATHY OF HORSES

The Proliferative Enteropathy (PE) of horses is a newly recognized enteric disease that affects -on most occasions- the weanling animals **(Williams et el 1996)**. Several animal species have been reported with PE including horses **(Lawson and Gebhart 2000)**. PE was described in the horse for the first time in a six-month-old Arabian foal **(Duhamel and Wheeldon, 1982)**. The authors intelligently described curved, rod-shaped organisms in the apical cytoplasm of the crypt epithelial cells which were the obligate intracellular bacteria causing severely devastating lesions in foals. Later, the etiologic agent of PE was identified using immunohistochemistry, PCR and Southern blot hybridization **(Williams et al.1996)**.

ETIOLOGY

When PE was described in horses for the first time, *Campylobacter spp* was thought to be the causative agent **(Duhamel and Wheeldon 1982)**. However when the second equine case was reported, the causative agent, *Lawsonia intracellularis*, has been well characterized in pigs.

L. intracellularis is an obligatory intracellular, gram negative, curved organism. The bacterium takes the acid fast **(Ziehl Neelsen stains)** but does not form spores **(McOrist et al. 1995)**. *L. intracellularis* grows only in a cell culture, intracellularly in enterocytes, and requires a microaerophilic atmosphere **(Lawson *et al.* 1993)**. It was found to be more closely related to the anaerobic human pathogen *Bilophila wadsworthia* based on the 16S rDNA testing **(Sapico *et al.* 1994)**. It was

thought that *L. intracellularis* is a non-motile and non-flagellated bacterium; however, examination using electron microscopy has shown that L. intracellularis possesses a long, single, unipolar flagellum **(Lawson and Gebhart 2000)**.

Inflammatory Bowel Disease in Human and *L. intracellularis*:

In human, inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) are known to be induced by multifactorial agent including infectious and genetic elements **(Bouma and Strober 2003, Greenstein 2003 and Ohkusa et al., 2004)**. The use of PCR utilizing *L intracellularis* -specific 16SII primers indicated that there is no association between IBD and *L intracellularis* **(Michalski et al., 2006)**. Since this organism is known to cause the disease in young animals, therefore it is unclear whether the age factor was responsible for the failure of detecting positive cases.

EPIDEMIOLOGY

Proliferative Enteropathy has been diagnosed in horse cases in North America before the year of 2003. Nevertheless, since then more PE cases are being reported in other parts of the world such as Australia and Europe **(McClintock and Collins, 2004)**. The increase of awareness among veterinarians may explain increased number of reports of the disease. Whether the diseases has been underdiagnosed or misdiagnosed in previous years, the difficulty in the diagnosis of PE might has contributed to the lack of information in the literature on equine PE. The mode of infection in the horse is not clear. However, the fact that several other species may be affected with PE complicates the epidemiology of the disease. PE-affected foals has been reported to shed *L. intracellularis* using fecal polymerase chain reaction (PCR) testing **(Lavoie et al 2000)**.

The vast majority of equine PE have been among individual animals, with the exception of outbreaks that affected three breeding farms in Canada **(Lavoie et al 2000)**. Additional study that looked at the incidence of the disease over a period of almost ten years showed that PE was the second most commonly diagnosed enteric pathogens after *Salmonella* in foals less than 12 months. This study also indicated that the disease was only detected in foals with enteric disorders **(Al-Ghamdi 2005)**.

CLINICAL SIGNS

The clinical manifestations of the disease in foals can be tricky. Clinical signs may include depression, anorexia, lethargy and diarrhea **(Williams et al 1996)**. The diarrhea may range in character from discolored soft feces to watery projectile diarrhea **(Duhamel and Wheeldon 1982, Frank et al 1998, Williams et al 1996)**. More sever disease characterized by fever and dehydration colic -mainly abdominal pain- may be seen early in the course of the disease **(Schumacher et al 2000)**. During an outbreak of PE Arabian and Thoroughbred foals, variety of signs were recorded including: poor body condition, emaciation, depression, weakness, ventral edema, anorexia, rough hair coat, cachexia, muscle fasciculation, dehydration, hyperemic mucus membranes, hypoproteinemia, watery diarrhea and death **(Lavoie et al 2000)**.

Foals experimentally infected with *L. intracellularis* had decreased appetite, colic, depression, diarrhea and dehydration **(Al-Ghamdi *et al*. 2002)**. The diarrhea was sever and watery. These signs were clearly observed as early as 14 days after challenge.

PATHOLOGY

Due to the fact that only a limited number of cases of PE were confirmed in horses in the literature, limited information on pathologic lesions of equine PE is available. In most of the reported cases gross pathologic lesions were localized in the small intestine **(Brees *et al* 1999, Duhamel and Wheeldon 1982, Frank *et al* 1998, Williams *et al* 1996)**. Diffuse and irregular thickening of the duodenum, jejunum, and ileum as a result of mucosal hyperplasia and transmural edema may be seen. In addition, the small intestine may have focal ulcerative lesions covered with feed and or fibrin. Such lesions varies between the jejunum and the ileum, with those in the mid-jejunum being multifocal with areas of discoid thickening. While those lesions in the distal jejunum and the ileum contain diffuse mucosal thickening forming a rugose pattern. Substantial lesions of the small intestine that included thickened wall of the jejunum and ileum as well as corrugated and hyperemic mucosa were described in experimentally challenged foals.

Significant thickening that consists of hyperplastic glandular structure can be seen in the affected mucosa during histopathologic examination. This hyperplasia results in change in the normal structure of the epithelium, resulting in an increase in proteinaceous fluid, cellular debris and neutrophils in the affected areas. The lamina propria may have a higher number of mononuclear cells. Functioning cells such as Paneth and goblet cells are reduced in affected areas **(Duhamel and Wheeldon 1982)**.

Clinical pathology may include increased fibrinogen, an indication of an ongoing inflammatory response **(Brees *et al* 1999, Frank *et al* 1998, Lavoie *et al* 2000)**. Additional inflammatory parameters can be indicative, such as an elevated band neutrophil count, elevated lymphocytes, and leukocytosis general. Serum biochemical analysis may show, hypoproteinemia -the most constant finding in PE affected animals-, hypoglycemia, hyponatremia, azotemia, elevated alkaline phosphatase and creatine kinase.

DIAGNOSIS

Clinical findings of PE in horses are not specific and may resemble other gastrointestinal diseases. Therefore, the clinical diagnosis of PE has been complicated to veterinarians since most diagnosis was based on postmortem examination of suspected cases. Gross and histologic findings of lesions in the small intestine area have been key elements in reaching diagnosis **(Duhamel and Wheeldon 1982, Frank *et al* 1998, Williams *et al* 1996)**. Warthin-Starry silver and Ziehl-Neelsen staining may detect the bacteria in the apical part of the cytoplasm of enterocytes during light microscopy examination. Electron microscopy is also used to visualize straight or curved bacilli within the cytosol of enterocytes. Immunohistochmesitry (IHC) utilizing monoclonal antibodies prepared against porcine *L. intracellularis* are used against intestinal tissue samples **(McOrist *et al* 1987)**.

Red-brownish IHC staining in the apical cytoplasm indicates affected intestinal cells. In the meantime, molecular approaches including polymerase chain reaction and Southern blot hybridization that specifically target a previously cloned DNA fragment of *L. intracellularis* were used to further confirm this finding.

DIFFERENTIAL DIAGNOSIS

Several viral, bacterial, parasitic, and non-infectious diseases have to be considered as a differential diagnosis for PE in foals **(Murray and Smith 2002)** Rotavirus has to be ruled out through electron microscopy of feces, ELISA, or latex agglutination tests can be used to rule out rotaviral infection. Equine adenovirus infection is most commonly seen in immunodeficient foals. Enteric bacterial agents such as *Salmonella* spp. *Clostridium* spp, *Neorickettsia risticii*, and *Rhodococcus equi* have to be tested for. Serial fecal cultures and/or detection of *Salmonella* DNA in feces using PCR are used to rule out enteric salmonellosis. N. risticii can be ruled out using serologic tests and on less occasions using PCR testing of blood samples to detect N. risticii DNA. Clostridium spp are ruled out using fecal culture for toxigenic clostridia, detection of clostridial toxins or toxic genes using PCR. Finally, parasitic diseases causing diarrhea, such as Cryptosporidia, should be ruled out using IFA and acid fast staining of feces of fecal flotation.

Non-infectious diseases causing diarrhea such as sand irritation, nonsteroidal drugs (NSAID), cantharidin toxicity, gastric ulceration, and antibiotic treatment have to be ruled out. This can be done by carefully questioning the owner and taking a complete history of the case.

TREATMENT

Despite the fact that limited work has been carried out on treatment of PE, the treatment can be rewarding if detected early (personal observation). Treatment should include specific and supportive therapy. Supportive intravenous fluid therapy is to be used to correct dehydration. Plasma transfusion is used to correct protein loss. Anti inflammatory agents such as flunixin meglumine, dexamethasone and prednisone are given to control inflammation. However, the use of corticosteroid therapy may be beneficial only in the initial phases and prolonged treatment has the risk of enhancing the disease. Antiulcer drugs such as cimetidine may be required. Antibiotic therapy is focused on the use of oral administration of combined erythromycin/rifampin, which is the treatment of choice to control *L. intracellularis* **(McOrist et al 1995)**. Other antibiotics such as chloramphenicaol and oxytetracycline has been used with some success on limited number of cases under field conditions but the risk has to be addressed.

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الملخص العربى

الاعتلال المعوى التكاثرى فى الخيل

غانم الغامدى

كلية الطب البيطرى والثروة الحيوانية، جامعة الملك فيصل، الأحساء، المملكة العربية السعودية

يعتبر مرض الاعتلال المعوى التكاثرى من الأمراض المصنفة حديثاً فى الخيل حيث تسببه بكتيريا اللاسونيا انتراسيلولاريس، أعراض المرض مستفارتة منها إرتفاع فى الحرارة نقص الوزن، إسهال والنفوق ويتمثل العلاج المناسب فى مضادات حيوية منها أيرثروماسين مع ريفامبين، والكلورامفينيكول أو أكسيتيتر اسايكلين مع مضادات الالتهاب مثل فلينوكسين ميجلومين ومضادات القرحة.