Mycobacterial Diseases
ISSN: 2161-1068

Monki and Hewetson,, J Mycobac Dis 2014, 4:2
DOI: 10.4172/2161-1068.1000147

Short Communication Open Access

Clinical Perspective: Intestinal Mycobacteriosis- A Rare Cause of Chronic Wasting Disease in Horses

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Rec date: Feb 12, 2014; **Acc date:** Mar 31, 2014; **Pub date:** Apr 05, 2014

Introduction

Intestinal mycobacteriosis is a chronic, progressive disease which can affect horses of all ages, and has been identified in weanlings as young as six months of age. The disease causes a granulomatous enteritis/enterocolitis. Clinical signs are non-specific, and include weight loss, diarrhoea, intermittent fever and dependent edema secondary to protein losing enteropathy (PLE). Intestinal mycobacteriosis should be considered as a differential diagnosis in any horse with chronic diarrhea, weight loss and/or a protein losing enteropathy. The condition appears to be rare in Europe and in other parts of the world; however the authors have personally diagnosed seven cases of intestinal mycobacteriosis in Finland between 2009 and 2013, suggesting an apparent increase in the incidence of the disease in recent years.

Epidemiology

The most common species responsible for mycobacterial infections in horses are members of the Mycobacterium avium complex [1] (Figure 1).

Figure 1: A rare cause of chronic wasting disease in horses

In contrast to cattle, only experimental infections of *M. avium* subspieces paratuberculosis have been established in horses [2], although clinical signs in horses may resemble Johne's disease in cattle [3]. *M. avium* ssp. *avium* and *hominissuis* appear to be the most common subspecies implicated in mycobacterial infections of horses [3]. In the past 25 years, mycobacteria have been reported to cause generalized infections [4-10], enterocolitis [11,12], interstitial pneumonia [1], guttural pouch infections [13], ocular infections [14], abortions [11,15], septic arthritis [16,17], vertebral osteomyelitis [18] and skin infections [19] in horses. Mycobacterial infections can also affect non-domestic equids as it has been reported in a captive-bred kiang [20].

Mycobacteria of the *M. avium*-intracellulare complex (MAC) have the capacity to survive in a wide range of environmental conditions [21], and because the organism is ubiquitous in soil it is commonly found in animal feed and bedding. *M. avium* ssp avium has also been isolated from a variety of insects and protozoa [21], and reservoirs for members of the MAC have been identified in wild animals. For example, *M. avium* ssp. hominisuis has been isolated from wild boar [21]. Generally, mycobacterial infections in horses arise via ingestion, although primary respiratory infection may occur [1]. The risk of zoonotic transmission from equine to human beings is considered to be quite small [3,22].

Mycobacterial infections are rare in horses [1], probably because the horse appears to possess a strong innate resistance to mycobacterial infections [3,22], and therefore an immunosuppressive state has been presumed to play a role in the development of the disease [7,23]. Most reported cases have been older horses and only three cases were two years of age or less [7,9]. In our case series, 4/7 (57%) horses were one year old or younger when the first symptoms were noticed. This is contrary to what has been reported in the literature, and may be explained by the late onset of endogenous IgGb production in foals (2-5 months), which has been suggested to be a predisposing factor for development of bacterial infections [24].

Clinical Signs

In previous case reports intestinal mycobacteriosis in horses, the major clinical findings have been chronic diarrhea [11,25,26] and weight loss [11,12,25,26]. The most common complaints in our case series were weight loss (7/7, 100%), chronic diarrhoea (7/7, 100%), pyrexia (6/7, 86%) and ventral oedema (6/7, 86%). Differential diagnoses to consider in young horses that present with these clinical signs include Lawsonia intracellularis [27] and Rhodococcus equi infection [28,29]. In weanlings, Lawsonia intracellularis infection is clinically indistinguishable from intestinal mycobacteriosis and is a much more likely cause of PLE. Cyathostomiasis [30], intestinal lymphosarcoma [31], chronic salmonellosis [32], right dorsal colitis [33] and inflammatory bowel disease [34,35] should be considered as differential diagnoses in adult horses [32].

In the authors´ experience, the most common clinicopathological finding in horses with intestinal mycobacteriosis were hyperfibrinoganaemia and hypoalbuminemia which were present in

7/7(100%) of cases examined. Other common abnormal findings included hypoproteinaemia (5/7,71%), leucocytosis (3/7,43%) and electrolyte disturbances (3/7, 43%).

Because mycobacteria cause granulomatous inflammation, histopathological changes are reported to be similar to idiopathic granulomatous enteritis in horses, which is a disease characterized by lymphoid and macrophage infiltration of the mucosal lamina propria with variable numbers of plasma cells and giant cells [36]. Idiopathic granulomatous enteritis most commonly affects young (1 to 5 year old) Standardbred horses [37,38] and acid-fast bacilli have been sporadically observed in the intestinal tissue of affected [11,12,25,37,39-41], suggesting that in some cases, this may in fact be the same disease.

Diagnosis

An ante-mortem diagnosis in horses can be challenging since clinical signs are non-specific [42]. Mycobacterial infections typically induce granulomatous inflammation; with or without multinucleated giant cells in the infected tissue [43]. These histopathological findings combined with a positive Ziehl-Nielsen stain identifying acid-fast rod-shaped organisms is considered diagnostic for mycobacterial infection [42].

An ante-mortem diagnosis in affected horses has been established by use of splenic and liver biopsies [6,38]. Rectal biopsy has also been recommended in cases of suspected intestinal mycobacteriosis [44]. In our case series, an ante mortem diagnosis was made in 2/3 (66%) horses in which a rectal biopsy had been obtained. In 2/7 (29%) cases, the submandibular lymph nodes were enlarged, thus a biopsy or aspirate of these lymph nodes might also have been useful in obtaining an ante mortem diagnosis.

Culture of mycobacteria can be challenging since it may take up to two months. Mycobacteria are intracellular organisms and may not be detected in faeces even with intestinal infection [38], thus tissue cultures should be performed. Additionally, M. avium spp. avium is considered an environmental rather than a pathogenic organism [45]. Therefore, mycobacteria can be found in faeces even though the animal is not infected. Isolation of mycobacteria in horses in clinical cases has been achieved in synovial tissue obtained during surgery [16,17] and non-healing skin ulcers [19]. Mair and Jenkins [46] also isolated mycobacteria from the nasal cavity of horses.

Polymerase chain reaction test for the detection of mycobacterial agents in diseased intestine of horses may be useful in determining the aetiology of granulomatous disease [1,4-6,19]. In cattle, diagnosis of Johne´s disease can be made by a faecal real-time quantitative PCR test, which has been proved as sensitive as culture [47]. The benefit of faecal PCR test is its ability to give a diagnosis rapidly. Resembling techniques would be of benefit in diagnosing MAC- infections in horses. In horses, M. avium ssp can be identified by multiplex PCR assays and restriction fragment length polymorphism analysis [48]. The tuberculin test is unreliable as tests may be positive in 70 per cent of clinically normal horses [49]. Serology can also be used to identify a rising antibody titer to mycobacteria [10] and may have potential as an ante-mortem test in horses. To the best of our knowledge, however, the current mycobacterium serological test is only able to identify M. avium ssp paratuberculosis (Map) antibodies, and it is currently not known if there is cross reactivity with other mycobacterium species. Furthermore, the low sensitivity and specificity of serology has traditionally been a problem with serological diagnosis of tuberculosis in human medicine [50] and is not commonly used. The usefulness of serology in horses with mycobacteriosis remains to be seen.

Treatment

Macrolides combined with rifampin are considered reasonable first choices for antimicrobial treatment for mycobacterial infections in horses [51], although the rationale for treating infected horses should be questioned, as the prognosis is invariably poor, even with prolonged broad spectrum antimicrobial treatment. In human infections with MAC- species, the use of macrolides has been shown to be crucial in cases that show response to treatment [52]. The use of rifampin in Finland is restricted for Rhodococcus equi infections in foals based on national drug legislation and therefore infected horses are not treated. Rather, an early ante mortem diagnosis and prompt euthanasia is preferred to avoid unnecessary treatment and prolonged suffering of the animals. Quarantine of suspected cases may be sensible however there is no data in horses suggesting that this is a transmissible disease.

Prognosis

All disseminated mycobacterial infections in horses have been reported to be fatal [1,4-14] and all 7/7 (100%) horses in our case series died or were euthanized.

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