Parasitic and zoonotic meningoencephalitis in humans and equids: Current knowledge and the role of *Halicephalobus gingivalis*

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ABSTRACT

Halicephalobus gingivalis is a saprophytic nematode parasite that causes a rare form of fatal meningoencephalomyelitis in equids, humans, and ruminants. This nematode has neurotropic activity, but has also been found in the kidney, liver, lungs, optic nerves and even heart of its host. Despite the zoonotic potential and severity of the disease, the epidemiology, pathogenesis, life cycle, and risk factors are poorly understood. Cases have been reported from several countries in Europe countries and North America but none is recorded in Africa except Egypt. This review looks at the historical overview, morphology, diagnosis, treatment and summary of reported cases in humans and equids. We recommend the parasitic helminthic infection in the differential list of meningoencephalitis involving humans and animals worldwide despite its rareness.

1. Introduction

Nematodes (round worms) are among the most diverse taxa in the animal kingdom with over 26,000 species described (Hugot et al., 2001). Nematodes are the most abundant soil metazoans (Bernard, 1992). Parasitic species may infect either animal (vertebrates and invertebrates) or man. Despite their diversity in terms of lifestyles, nematodes share a general common anatomy and physiology.

Halicephalobiasis is a helminthic infection caused by *Halicephalobus gingivalis*. The latter is a free-living soil saprophytic nematode known to cause opportunistic infections in the form of fatal meningoencephalomyelitis mainly in equines. *Halicephalobus gingivalis*, also known as *Micronema deletrix*; *Halicephalobus deletrix* belongs to the nematode Order *Rhabditida*, Family Paragrolaimidae. Currently, there are eight described species of *Halicephalobus*, and only *H. gingivalis* has been reported to infect humans and equines - predominantly in horses (Anderson et al., 1998) and to a lesser extent zebras (*Equus grevyi*) (Isaza et al., 2000) and donkeys (Schmitz and Chaffin, 2004). Recently, *H. gingivalis* has been reported to cause bovine meningoencephalomyelitis in ruminants (calves), where parasites were identified morphologically and diagnosis confirmed by molecular analysis of the large subunit (LSU) and small subunit (SSU) rRNA genes of the parasite (Enemark et al., 2016). Other species within the genus *Halicephalobus* include *H. limuli*; *H. similigaster*; *H. minutum*; *H. parvum*; *H. palmaris*; *H. intermedia* and *H. laticauda* (Anderson et al., 1998).

The organism is commonly referred to by its generic name, because the species are difficult to distinguish morphologically (Ondrejka et al., 2010) although, the shape of the tail and descriptions of the reproductive tract seem to distinguish *H. gingivalis* from other species in the genus. Only parasitic female adults, larvae and eggs have been isolated from parasitized hosts, confirming that *H.*

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gingivalis can reproduce parthenogenetically, although how *H. gingivalis* infects human and equine hosts is still largely speculative (Papadi et al., 2013). In the environment, *H. gingivalis* has been isolated from horse manure and compost (Steel et al., 2010).

Human infections are very rare, but all cases described to date involved fatal meningoencephalitis (Lim et al., 2015) and of the reported equine cases only four horses have survived (Dunn et al., 1993; Pearce et al., 2001; Schmitz and Chaffin, 2004; Muller et al., 2008). The success of this parasite in causing its pathology may be unconnected to its mode of reproduction. Current reports have demonstrated the presence of this parasite in localities where it was presumed to be absent. This review aims to provide more light on this silent but potentially zoonotic parasite causing fatal meningoencephalitis in humans and equids around the world and the need to develop a diagnostic tool to diagnose the infection antemortem as majority of the diagnosis has been at postmortem.

2. Parasite biology

2.1. Historical perspective

Stefanski (1954) was the first to accurately describe the nematode. He found the worms in a granuloma in the gingivae of a horse in Poland. He first placed the species in the genus *Rhabditis*. It was later transferred to the genus *Tricephalobus* by Dougherty (1955). Sudhaus (1976) placed *gingivalis* in *Trilabiatus*. Later, Andrassy (1952) placed the species in *Halicephalobus* where it remains till date. Anderson and Bemrick (1965) described *Micronema deletrix* from a nasal tumour of a horse in Minnesota, USA. The clinical pathology of this case was later described by Johnson and Johnson (1966) who reported the nematodes mainly in large granulomas in the maxillae. Andrassy (1952) and Geraert et al. (1988) in reviews of the genus *Halicephalobus* apparently regarded *H. deletrix* as a possible synonym of *H. gingivalis*. Although they gave no reasons for this possibility it can probably be assumed that it was because *H. gingivalis* and *H. deletrix* were both from lesions in horses.

2.2. Morphology

The typical morphologic features of *Halicephalobus deletrix* are the distinctive rhabditiform esophagus with corpus, isthmus, and bulb and their reproductive tracts are didelphic with dorsiflexed ovaries at the posterior end. Only female worms are found in tissue. Adult female worms are 250 to 460 μm by 15 to 25 μm. The larvae stages are smaller and have the same features as the fully developed worms but lack a reproductive system. The larvae are 250 to 300 μm long and 15 to 20 μm wide, with a rhabditoid esophagus (70 to 90 μm long). Eggs are oval, elongated, thin-shelled and colorless 40 to 55 μm by 20 to 25 μm in size (Lim et al., 2015). This nematode characteristically lacks lateral or cuticular alae. The cuticle of the worm is thin and has fine striations (Gardiner et al., 2000).

2.3. Life cycle

The life cycle of *Halicephalobus* sp. is poorly understood. But it is believed that the adult female worm reproduce asexually by parthenogenesis. Asexual reproduction is usually considered as an evolutionary dead end, and difficulties for asexual lineages to adapt to a fluctuating environment are anticipated due to the lack of sufficient genetic plasticity (Castagnone-Sereno and Danchin, 2014). This mode of reproduction is common among nematodes of the order Tylenchida and Rhabditida. When a female reproduces using parthenogenesis, she has no need for a male. This means that a parthenogenetic female can spend more time and energy seeking food and shelter while such resources are readily available. Without the need for males, parthenogens can reproduce faster than species that reproduce sexually. In fact, a group of parthenogenetic females can produce a certain number of offspring with only half as many parents as a similarly sized group of sexually reproducing animals. Surprisingly, only the females - usually found in association with eggs and immature larvae - have been identified and characterized from tissue samples till date (Lim et al., 2015).

2.4. Phylogenetics of Halicephalobus gingivalis

A recent study carried out by Pintore et al. (2017) revealed that the *H. gingivalis* isolates belonged to Lineage 3, which includes other isolates from Japan and USA. Only a few sequences are available on public databases, with little information on date of sample collection and location. However, the sequence similarity data and phylogenetic analysis confirm that there is no correlation between location and genetics in *H. gingivalis* based on 28S rRNA gene data. Furthermore, there was no apparent correlation between lineages and clinical manifestation of *H. gingivalis*, although the number of available sequences is limited (Nadler et al., 2003). Notably, the only two *H. gingivalis* sequences available from human cases are those recently reported in Australia and Germany (Lim et al., 2015; Monoranu et al., 2015). Both were classified by phylogenetic analysis as belonging to Lineage 1. Sequencing of more isolates and the analysis of multiple loci will help in establishing a correlation between phylogenetic clustering, geographic correlation, clinical signs and the zoonotic potential of *H. gingivalis*. Genetic variation study was used to distinguish the *H. gingivalis* isolated from Danish calves to published isolates by comparing the large subunit (LSU) rRNA and the small subunit (SSU) rRNA genes of *H. gingivalis*, which was found to have a genetic variation of 0.5% - 4.4% and 0.7–8.6%, respectively (Enemark et al., 2016).
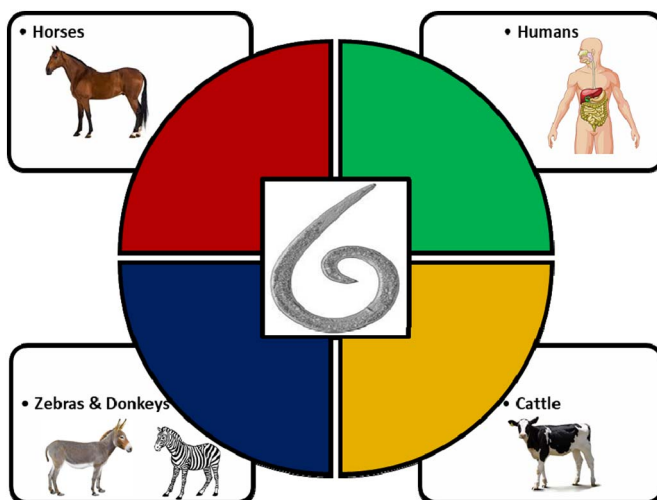
Fig. 1. Reported host organism infected by *Halicephalobus gingivalis*.

3. Epidemiology

3.1. Host range

Though, this worm is known to be saprophytic and free-living in humus soil. It has been reported to infect and become parasitic in horses, humans, zebras, donkeys, and recently in ruminants (cattle) where it causes fatal granulomatous and neurological lesions. A schematic presentation of host range is presented in Fig. 1 below.

3.2. Distribution

It has a worldwide distribution but majority of the reports in humans and equids so far have been in Europe, North America and North East Asia. Only one documented report was from Africa. Geographical spread is presented in the map below (Fig. 2) and in Tables 1 and 2 below.
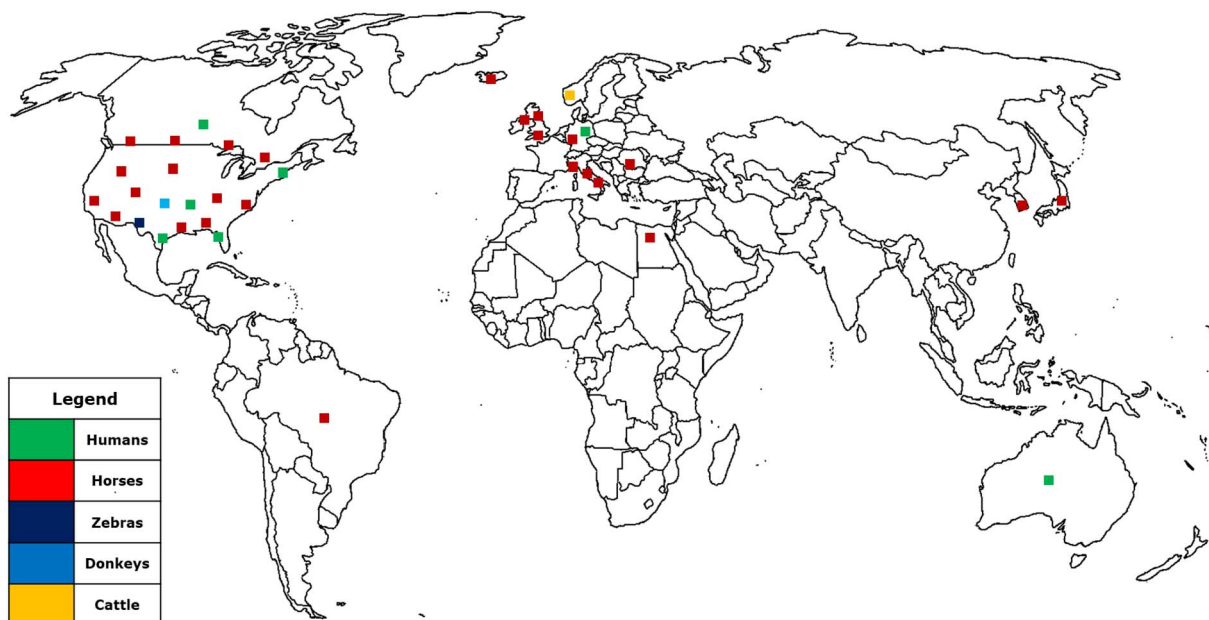

Fig. 2. World map showing the geographical distribution of Halicephalobiasis in animals and humans.

3.3. Mode of infection and predilection sites

The method of infection is unclear but it is presumed to be contamination of oral mucosa or skin wounds (Anderson et al., 1998). It is presumed that the nematodes enter the tissues through wound lesions and are carried to other parts of the body through haematogenous route in blood and lymph (Henneke et al., 2014) or through the optic nerve – optic tract and that the contamination of ocular wounds would be the entrance (Rames et al., 1995). Transmammary infection from mare to foal has been reported once (Wilkins et al., 2001). The larvae has been demonstrated in urine samples (Taulescu et al., 2016), and a fly (*Musca autumnalis*) has been proposed as carrier of larvae (Anderson et al., 1998). Viable *Halicephalobus* organisms have been detected and isolated from in semen (Kinde et al., 2000), though no transmission via this route has been proven, it is another possible source of infection. *H. gingivalis* gets access to the central nervous system via blood vessels, causing necrosis and inflammation due to visceral migration (Kreuder et al., 1996). The brain is the most commonly involved site, followed by other organs such as the kidneys, oral and nasal cavities, lymph nodes, spinal cord and adrenal glands. Infections involving the heart, stomach, liver, ganglion and bone have also been reported (Spalding et al., 1990; Kreuder et al., 1996). Massive intracranial invasion in horses is acute and of short duration (Jubb and Huxtable, 1993).

4. Diagnosis

Diagnosis of *Halicephalobus* sp. infection in humans and animals involves a combination of various methods. So far, no specific antemortem diagnosis technique is available for specific diagnosis of the disease in humans and animals. But a combination of magnetic resonance imaging (MRI), haematology and serum biochemical parameters has been evaluated in previous report. Furthermore, gross and histopathological lesions have been observed from affected tissues/organs in infected animals and humans at postmortem. Molecular technique such as Polymerase chain reaction (PCR) in detecting parasite DNA in brain tissues collected at post mortem have been specific. So far, no specific antemortem diagnostic technique has been developed for diagnosis. Therefore, there is an urgent need to develop a tool which will be rapid and specific for the diagnosis of suspected cases of meningoencephalitis.

5. Treatment

Anthelmintic therapy has been used with limited effect to alleviate signs of infection with *H. gingivalis* in horses (Rames et al., 1995; Pearce et al., 2001; Ferguson et al., 2008), and in clinical cases involving the CNS treatment was particularly inadequate (Ferguson et al., 2008; Umlauf et al., 2012). Treatment responses in previous cases in animals, shows that most affected animals deteriorated (Ruggles et al., 1993; Trostle et al., 1993; Rames et al., 1995; Kinde et al., 2000; Isaza et al., 2000 and Ferguson et al., 2008) despite treatment and the presence of live worms at autopsy suggests that the anthelmintic treatment was ineffective. None of the reported human cases received anthelmintics (Hoogstraten and Young, 1975; Shadduck et al., 1979; Gardiner et al., 1981; Ondrejka et al., 2010 and Lim et al., 2015). In vitro susceptibility testing using microagar larval developmental tests (MALDTs) has been used to assess the effects of thiabendazole and ivermectin on the hatching rate and larval development of *H. gingivalis* (Fonderie et al., 2012). Thiabendazole at concentrations of 10 to 100 μg/ml showed a dose-dependent inhibition effect on the hatchability of eggs. However, no inhibition of larval development was observed. Thus, *H. gingivalis* appears to have some intrinsic tolerance of ivermectin, but larval development can be temporarily suppressed at 2 μg/ml. Pharmacokinetic studies have showed that ivermectin rarely enters the CNS since it is actively removed by the P-glycoprotein, an abundant transporter protein in the brain. This can result in an undetectable CSF level, despite a parenteral dose of 200 μg/kg of body weight, which is often used for disseminated *S. stercoralis* infection (Nau et al., 2010). Treatment has not been described in human cases, but pharmacokinetic studies suggest that treatment with ivermectin or thiabendazole administered parenterally may not be effective because of poor killing effect per se and inability to achieve therapeutic levels in CNS (Fonderie et al., 2012).

6. Prevention and control

No specific control measures have so far been developed. This is because limited information is available concerning the epidemiology of the infection. Overall, it is recommended that good pasture management and prevention of horses from marsh or swampy environment. Humans working in soils and handling stable waste should wash hands regularly with regular deworming.

7. Pathological findings

The predominant inflammatory cells are plasmocytes and lymphocytes, occasional eosinophils and numerous macrophages, giant cells and epithelioid cells (Rames et al., 1995). Similar inflammation was observed, in systemic infections, in the kidneys (Isaza et al., 2000; Kinde et al., 2000), lymph nodes, uterus and heart (Isaza et al., 2000), testicles (Kinde et al., 2000), stomach, lungs, joints, adrenal gland (Simpson et al., 1988), prepuce (Dunn et al., 1993), bones (Kreuder et al., 1996; Teifke et al., 1998) and the spinal cord, the roots of the peripheral nerves and the *cauda equina* (Johnson et al., 2001). The predominant localization of the rhabditiform larvae is perivascular. Many authors report the presence of larvae, adult worms and eggs in the granulomatous lesions of *H. gingivalis* (Lim et al., 2015; Ondrejka et al., 2010). This fact would be a criterion to differentiate it from *Strongyloides* sp. Besides the different morphology, eggs and adult parasites are not seen in the cutaneous lesions of the horse (Dunn et al., 1993).

Table 1
Reported cases of *Halicephalobus gingivalis* infection in equids between 1972 and 2017.

Year	Specie	Country	Clinical presentation	Diagnosis	Reference
1972	Horse	Egypt	Encephalitis	Post mortem	Ferris et al. (1972)
1987	Horse	United Kingdom	Encephalitis	Post mortem, morphological	Blunden et al. (1987)
1990	Horse	United States	Encephalitis, spinal cord lesions	Post mortem, morphological	Spalding et al. (1990)
1992	Horse	Scotland	Encephalitis and renal abscess	Post mortem, morphological	Angus et al. (1992)
1993	Horse	United States	Encephalitis, osteomyelitis	Morphological	Ruggles et al. (1993)
1993	Horse	United States	Encephalitis	Morphological	Trostle et al. (1993)
1993	Horse	United States	Prostitis	Morphological	Dunn et al. (1993)
1995	Horse	United States	Encephalitis	Morphological	Rames et al. (1995)
1998	Horse	Germany	Osteomyelitis gingivitis	Morphological	Teifke et al. (1998)
2000	Horses	United States	Encephalitis, nephritis	Morphological	Kinde et al. (2000)
2000	Grevy's zebra (*Equus grevyi*)	United States	Ocular infection	Morphological	Isaza et al. (2000)
2000	Horse	Canada	Encephalitis	Post mortem, morphological	Brojer et al. (2000)
2001	Horse	United States	Encephalitis	Post mortem, morphological	Wilkins et al. (2001)
2001	Horse	United States	Encephalitis	Post mortem, morphological	Johnson et al. (2001)
2001	Horse	Canada	Encephalitis	Morphological	Pearce et al. (2001)
2004	Donkey	United States	Renal abscess	Morphological	Schmitz and Chaffin (2004)
2006	Horse	United States	Encephalitis	Post mortem, morphological	Bryant et al. (2006)
2007	Horse	Japan	Encephalitis, nephritis	PCR	Akagami et al. (2007)
2007	Horse	Brazil	Neurological sign	Post-mortem, histopathology	Vasconcelos et al. (2007)
2008	Horse	Switzerland	Prostitis	Morphological	Muller et al. (2008)
2008	Horse	Canada	Encephalitis, mandibular abscess	Morphological	Ferguson et al. (2008)
2011	Horse	United Kingdom	Encephalitis	Post mortem, morphological	Hermosilla et al. (2011)
2011	Horse	Canada	Encephalitis	Post mortem, morphological	Sponseller et al. (2011)
2012	Horse	Iceland	Encephalitis	Post mortem, morphological	Eydal et al. (2012)
2012	Horse	Italy	Encephalitis	Post mortem, morphological	Di Francesco et al. (2012)
2014	Horse	South Korea	Encephalitis	PCR	Jung et al. (2014)
2016	Horse	Romania	Encephalitis	PCR, morphological	Taulescu et al. (2016)
2016[a]	Cattle	Denmark	Encephalomyelitis	PCR, morphological	Enemark et al. (2016)
2017	Horse	Italy	Encephalitis	PCR, morphological	Pintore et al. (2017)

[a] An exception on the list- this is the first and so far, the only reported case of *Halicephalobus gingivalis* infection in dairy cattle.

7.1. Gross lesions and neurological changes due to Halicephalobiasis in equids

Infections caused by *Halicephalobus* sp. are seldomly encountered in equine veterinary practices. Infections in horses cause granulomatous lesions and extensive tissue destruction that most commonly affect the central nervous system (CNS), skin, and kidneys (Ondrejka et al., 2010). The clinical manifestations include nasal tumor involvement (Anderson and Bemrick, 1965), osteomyelitis (Kreuder et al., 1996). granulomatous prepuce infection (Muller et al., 2008), granulomatous nephritis (Akagami et al., 2007), meningoencephalitis (Akagami et al., 2007), and occasionally disseminated disease (Ruggles et al., 1993). Several equine cases involving the CNS were presented with ataxia, all of which culminated in euthanasia or death by overwhelming infection (Bryant et al., 2006; Brojer et al., 2000). Furthermore, changes in the brain such as lymphohistiocytic meningoencephalitis were most prominent in the thalamus, internal capsules, and midbrain. Nematodes were occasionally seen in the tunica media, small arteries and meninges. The nematodes from the affected horse were cultured and identified morphologically as *Halicephalobus gingivalis* (Brojer et al., 2000). A summary of the reported cases so far of the infection in horses from 1987 to 2017 are presented in Table 1 below.

7.2. Gross lesions and neurological changes due to Halicephalobiasis in Humans

Involvement of the brain is one of the most outstanding clinical manifestations of this disease in humans with fatal consequences. The most consistent observation relates to the central nervous system notably meningoencephalomyelitis. Clinical symptoms common to these cases include change in mental status, lethargy, and fever. Cerebrospinal fluid studies were reported in 4 of the 7 previous patients and showed an elevated white blood cell count with a lymphocytic predominance. The distribution of the disease has consistently included the meninges and parenchyma, with a myelitis component recognized in half of the patients (Ondrejka et al., 2010). Juvenile forms of the nematodes have also been found in pulmonary capillaries in sections of the lungs, but it is believed that the worms were carried to the lungs from the CNS not the reverse (Hoogstraten and Young, 1975). The worm has been reported in the liver and lungs with infiltration of inflammatory cells and no cellular response respectively (Gardiner et al., 1981). Other gross pathologic findings include edema, focal hemorrhage, and variable evidence of necrosis. The typical histopathologic pattern is that of predominantly perivascular acute and chronic inflammation, including multinucleated giant cells. Most reports describe regions of gliosis or glial cellular proliferation. In some instances, a more intense inflammatory infiltrate occasionally accompanied by granulomatous inflammation has been observed in association with the organisms themselves. Biopsy performed on the right temporal lobe showed chronic active meningoencephalitis with focal chronic granulomatous vasculitis (Ondrejka et al., 2010). Mild cerebral

Table 2
Reported human cases of *Halicephalobus gingivalis* infection between 1975 and 2017.

Year	Demography	City/country	Clinical presentation	Diagnosis	Reference
1975	5 years old, male	Manitoba, Canada	Meningoencephalitis, mandibular injuries	Post mortem	Hoogstraten and Young (1975)
1979	47 years old, male	Texas, United States	Meningoencephalitis, brainstem signs	Post mortem	Shadduck et al. (1979)
1981	54 years old, male	Washington, United States	Bilateral internuclear ophthalmoplegia.	Post mortem	Gardiner et al. (1981)
2010	39 years old, female	Kentucky, United States	Meningoencephalitis, bilateral ring enhancing lesions	Post mortem	Ondrejka et al. (2010)
2013	65 years old, female	Florida, United States	Encephalopathy, blurring of vision	Post mortem	Papadi et al. (2013)
2014	74 years old, female	Eyre Peninsula of South Australia	Meningoencephalitis, frontoparietal meningitis	Post mortem	Lim et al. (2015)
2015	49 years old, no sex indicated	Würzburg, Germany	Meningoencephalitis	Post mortem	Monoranu et al. (2015)

atrophy and chronic ischemic changes have also been recorded using computed tomography and magnetic resonance imaging respectively of the brain of an affected human. Results of an electroencephalogram of an affected patient showed moderate diffuse slowing of electrocerebral activity, suggestive of encephalopathy of toxic, metabolic or degenerative nature (Papadi et al., 2013). Furthermore, microscopic examination of brain, spinal cord, and meninges also showed extensive inflammation and nematodes morphologically consistent with *Halicephalobus* sp. (Papadi et al., 2013). Finally, gross lesions that have been observed include restricted lateral ventricles, sub-facial herniation of the right enlarged hemisphere, and symmetrical cerebellar herniation. A summary of reported cases so far of the infection in humans from 1975 to 2017 are presented in Table 2 below.

8. Current situation in Africa

To the best of our knowledge, only one report so far was made in Egypt (Ferris et al., 1972). So far, no reported case of halicephalobiasis has been made in west and east Africa. That does not mean it may not have happened or occurred in these regions. Poor state of disease surveillance and diagnosis may mask the situation on ground. It is therefore expedient that proper institutional framework be put in place to curtail and prevent diseases generally of equine. Findings from close conversation with horse owners in Nigeria underscore the need for a collaborative and synergistic effort to improve proper disease prevention, diagnosis, and management in equine and by extension to prevent zoonotic outbreaks in humans.

9. Final perspective

Diseases have no boundary and the International movement of humans and horses could facilitate the transmission of diseases. The horse racing and polo sports are becoming popular in Nigeria, and in most African countries, where horses are transported from a part of the country or continent to another. In Nigeria, horse riding and polo sports are mainly undertaken by the wealthy. Huge amount of money are spent annually to import horses from different parts of the world, most especially from Europe and North America. Equine veterinary practitioners are few in Nigeria and most of the horse owners depend on services from local quacks or veterinary assistants for the management of their horses. From the current situation with equine practice, many diseases of horses are either misdiagnosed or not properly managed. There is the need for a more concrete and collaborative efforts by the local authorities to put adequate measures in place to prevent or forestall any undesirable consequences. Halicephalobiasis, although extremely rare, could be a fatal disease that may result to mortality and morbidity in both in equines and humans, respectively. We recommend that Halicephalobiasis should be considered as a potential cause of parasitic meningoencephalitis in cases of infection affecting equines and humans in worldwide and proper diagnosis should be intensified.

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