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AFRICAN TRYPANOSOMIASIS WITH SPECIAL REFERENCE TO EGYPTIAN TRYPANOSOMA EVANSI: IS IT A NEGLECTED ZOONOSIS?

By
MAMDOUH M. M. EL-BAHNASAWY[1], MAI KH. A. KHATER[1] AND TOSSON A. MORSY[2]
Military Medical Academy[1] and Department of Parasitology, Faculty of Medicine, Ain Shams University, Cairo 11566[2], Egypt

Abstract

Trypanosomes (including humans) are blood and sometimes tissue parasites of the order Kinetoplastida, family Trypanosomatidae, genus *Trypanosoma***,** principally transmitted by biting insects where most of them undergo a biological cycle. They are divided into Stercoraria with the posterior station inoculation, including *T. cruzi***,** both an extra- and intracellular parasite that causes Chagas disease, a major human disease affecting 15 million people and threatening 100 million people in Latin America, and the Salivaria with the anterior station inoculation, mainly African livestock pathogenic trypanosomes, including the agents of sleeping sickness, a major human disease affecting around half a million people and threatening 60 million people in Africa. Now, *T. evansi* was reported in man is it required to investigate its zoonotic potential?

Key words: African trypanosomes, *Trypanosoma evansi,* Review

Review and Discussion

The African trypanosomiasis (sleeping sickness) is endemic throughout much of the sub-Saharan Africa. The countries with the highest endemicity include Angola, Cameroon, Central African Republic, Chad, Congo, Cote d'Ivoire, Democratic Republic of Congo, Guinea, Mozambique, Sudan, Tanzania, and Uganda. The prevalence of trypanosomiasis in many countries is active increasing. The two different species of the parasite cause two epidemiologically distinct diseases: West African trypanosomiasis is caused by *T. brucei gambiense*, humans are the primary reservoir, it occurs mainly in wooded areas along rivers, and tourists are rarely infected. The Eastern African trypanosomiasis is caused by *Trypanosoma b. rhodesiense,* antelope and cattle are the primary reservoirs, it occurs mainly in savanna and woodland areas, and has been reported in tourists visiting game parks. Both parasites are transmitted by *Glossina* spp. (Ponce-de-Leon *et al*, 1996). Transplacental infections have been described in *T. equiperdum* and *T. gambiense* (Sina *et al,* 1979). Also, vertical transmission of *T. evansi* has also been demonstrated in several instances, as shown in a review on transplacental transmission (Ogwu *et al*, 1981). *Trypanozoon*, especially *T. evansi*, may be transmitted by oral contamination. This mechanism could damage quite easily oral mucosae.

Clinical Features: Both Gambian and Rhodesian HAT are characterized by an early stage, during which trypanosomes are found circulating in the blood or in lymph nodes, and a late stage in which there is prominent involvement of the central nervous system (CNS). However, the clinical picture of *T. b. gambiense* is different from *T. b. Rhodesiense*. *T. b. gambiense* is a slowly progressive infection, and the asymptomatic phase lasts for months or years. In contrast, *T. b. rhodesiense* progresses rapidly, and CNS affection is often detectable within weeks. Both infections are fatal if untreated.

Desquesnes *et al*. (2013) reported that *T. evansi* has a more complex epidemiology due to the diversity of its hosts and vectors, with difficult impact of clinical and subclinical disease. A model was developed for buffaloes in the Philippines, which could be transferred to other places and livestock systems. Since zoonotic *T. evansi* was reported, more research is required to investigate its epidemiology. Surra remains a potentially emerging disease threats to France, Australia

and Spain.

Chancre: The first sign of infection with either type of African trypanosome may be an acute inflammatory lesion, trypanosomal chancre, which typically appears approximately a week after the bite of an infected tsetse fly. This is usually a well-circumscribed, rubbery, painful, indurated, red papule 2 to 5 cm in diameter. It is seen more frequently with *T. b. rhodesiense* than *T. b. gambiense*. The chancre usually resolves spontaneously after several weeks, but it can ulcerate (Hope-Rapp *et al*, 2009). Patients can also present with transient, erythematous, urticarial, or macular rashes six to eight weeks after the onset of illness. The lesions can manifest as poorly defined, centrally pale, evanescent, annular, or blotchy erythematous macules on the trunk or trypanids (Mallewa and Wilmshurst, 2014)

Lymphadenitis: Trypanosomes then travel to regional lymphatics, where they proliferate and cause lymphadenitis. In *T. b. gambiense*, lymphadenopathy typically occurs in the posterior cervical nodes; these soft, painless, mobile nodes are classically referred to as Winter-bottom's sign. But, lymphadenopathy can develop at any site. Lymph node enlargement is less frequently with *T. b. rhodesiense*. However, when lymphadenopathy is present, nodes in the submandibular, axillary or inguinal region are more often involved rather than cervical (Wengert *et al*, 2014).

In *T. b. gambiense* early symptoms include intermittent headache, fevers, malaise, and arthralgias. These symptoms are frequently intermittent, corresponding with successive waves of the parasitemia and antibody production. The organomegaly, in particularly splenomegaly, is a common finding. Generalized lymphadenopathy is also often present. Pancarditis occasionally develops leading to arrhythmias and/or cardiac failure. This presumably arises from perivascular infiltration by trypanosomes and lymphocytes, resulting in endarteritis and secondary fibrosis. Other nonspecific symptoms may be present, including pruritus, rash, weight loss and facial swelling. The neuroendocrine disturbances leading to amenorrhea in women or impotence in men may also be seen.

Brain involvement: In later stages of *T. b. gambiense*, progressive diffuse meningoencephalitis and parenchymal edema of the brain develop. Perivascular and meningeal inflammatory infiltrates, cerebral hemorrhages and widespread multifocal white matter demyelination occur. Symptoms include headache, difficulty concentrating, personality changes, psychosis, sensory disorders, tremor and ataxia. Meningismus and focal neurologic signs may occur but unusual. An alteration of the circadian sleep/wake cycle leading to daytime somnolence also frequently develops. Convulsions may occur, especially in children. Progressive deterioration occurs until patient is in a stuporous state. At this stage, cachexia, wasting and malnutrition develop as they are too drowsy to eat. Patients are also at risk for complications such as aspiration pneumonia and secondary bacterial infections.

A similar sequence of events is seen with *T. b. rhodesiense*, but the presentation and progression are typically much more rapid. Rather than asymptomatic periods and slow deterioration, Rhodesian trypanosomiasis causes an acute, severe febrile disease that rapidly progresses to involve the CNS over weeks to a few months. Worsening coma and death ultimately occur in both infections (Kibugu *et al*, 2009).

Truc *et al*. (2014) stated that some trypanosomes natural parasites only of animals can sometimes infect humans and cause the atypical human trypanosomiases (aHT). *T. evansi*, the agent causing surra in camels, horses, dogs, and bovines, and *T. lewisi*, a cosmopolite rat parasite, are the most frequently involved. The aHT involved no or only minor symptoms, but major symptoms are sometimes present. The prevalence was underestimated. Besides, these trypanosomes might become potential emerging zoonotic disease due to ability to invade new hosts.

Diagnosis: Thick peripheral blood smears stained with Giemsa or direct thin smears may show trypanosomes. The sensitivity of blood smears varies with the stage of disease and the infecting species. Smears are more likely positive in early stages of infection when there are high numbers of circulating parasites, as well as more likely positive in *T. b. rhodesiense* infection, since this species is associated with higher levels of parasitemia. The levels of parasitemia fluctuate; repeat smears should be done on consecutive days if the initial test is negative. Thick smears can detect parasites at least 5000/ml.

Blood concentration techniques by using hematocrit centrifugation increase the sensitivity but require technical expertise. A quantitative buffy coat (QBC) technique which uses centrifugation and a fluorescent stain to identify motile trypanosomes can also be used. Another concentration technique is a minianion exchange column (mAECT). Blood is filtered through resin that retains blood but let's the trypanosomes pass through; the eluate is then centrifuged and examined microscopy. It can detect parasitemia down to levels of 5parasites/ml. but not widely available in endemic areas (Lumsden *et al*, 1981).

For patients with lymphadenopathy, the lymph node aspirate may reveal motile parasites by direct microscopy; trypanosomes may also be seen after fixation and staining with Giemsa. As lymphadenopathy is more common in Gambian form, this method is a traditional diagnostic and screening method in *T. b. gambiense* infection. A chancre aspirate may also reveal trypanosomes in patients with this skin lesion. Bone marrow aspirates may be positive for parasites in some patients (Lejon and Buscher, 1995).

Elsen *et al*. (1990) reported *Glossina fuscipes fuscipes* and *G. morsitans submorsitans* from southwestern Saudi Arabia. Meltzer *et al.* (2012) in Israel reported *T. brucei rhodesiense* in a traveler returning from Tanzania with a relapsing febrile illness, and diagnosis was established by blood smear after nearly a month.

Kong *et al*. (2012) found that specificity of the 529 bp-LAMP assay was determined using the DNA samples of *T. evansi*, *Plasmodium falciparum, Paragonimus westermani, Schistosoma japonicum, Fasciola hepatica* and *Angiostrongylus cantonensis*, without cross-reactivity with DNA of any parasite.

Sengupta *et al*. (2014) stated that *T. evansi* causes surra an important chronic wasting disease of a wide range of wild and domestic herbivorous and carnivorous animals including cattle, buffaloes, camels, horses as well as rodents…etc. Untreated recovered animal could act as a carrier without any symptoms and can be a source of infection to healthy ones. They added that developed recombinant antigen can be a diagnostic tool for carrier animals and disease control. Mandal *et al*. (2014) found that the liver and lung impression smears could detect the parasites up to 14 hr. of post-death of mice and rats and up to 13 hr. post-death of rabbits whereas spleen impression smears revealed the presence of parasites up to 12 hr. post-death of all these animals, and that *T. evansi* infection in animals was diagnosed after post-mortem examination of hosts for parasites. In water buffalo, *T. evansi* causes production losses, abortion, early calf mortality, and has immunosuppressing effects that decrease efficacy of some vaccines (mainly vaccine for hemorrhagic septicaemia). Bovine's pathogenicity in Asia is more dangerous than that caused by either the African or American strains (Villareal *et al*, 2013).

Sharma *et al*. (2014) reported that duplex PCR consisting of two primer sets within a single mixture for simultaneous detection of *Anaplasma marginale* and *T. evansi* was standardized and employed on 219 blood samples from cattle and buffaloes from eastern Punjab to evaluate the status of concurrent infection and associated risk factors. The reaction produced 257- and 407-bp amplification products targeting repetitive nucleotide sequence of *T. evansi* and msp1β gene of *A. marginale*, respectively.

In Egypt none reported any species of *Glo-*

ssina the African trypanosomiasis vector, but only *Ta banus* species and *Stomoxys* species, vector of camel *T. evansi* (Rodríguez *et al*, 2014). Steyskal and El-Bialy (1967) identified ten species of *Tabanus* and Morsy and Habib (2001) identified two more species. *S. calcitrans* is well known in Egypt (Hafez and Gamal-Eddin, 1959; Steyskal and El-Bialy, 1967).

On the other hand, *T. evansi* is multiples in the blood and body fluids. The incubation period varies from 7-15 days. The mortality rate was up to 20% and fatality rate may reach up to 100% in untreated camels.

Haridy *et al*. (2011) detected *T. evansi* in a worker caring for camels as indicated by *T. evansi* ELISA-antibodies and the presence of *T. evansi* in stained blood smears. The human case was successfully treated as indicated clinically, parasitologically and serologically. They concluded that animal trypanosomiasis especially that of camels should be in the concern of the Veterinarian and Medical Health Authorities.

The clinical signs and symptoms in camels are unreliable for sharp diagnosis. Camels with acute infection have a short clinical course and die within weeks to months of infection. But, some chronic cases persist for years (Sengupta *et al*, 2014).

Mechanical transmission by biting insects (as *Tabanus, Stomoxys* and others) is the most important mode of transmission of *T. evansi* in camels, as well as in livestock and other large animals generally. The mechanical transmission is a nonspecific process occurs by interrupted feeding of many other blood sucking insects (Desquesnes *et al*, 2009).

In Africa *T. evansi* is present in all countries where camels are present, north of a line extending from Senegal (15° North) to Kenya (equator), above the tsetse belt; it is found not only in Algeria, Egypt, Eritrea, Ethiopia, Libya, Mauritania, Morocco, Sudan, and Tunisia, but also in the northern parts of Mali, Burkina Faso, Niger, Nigeria, Chad, Somalia, and Kenya.

Nowadays, its geographical distribution is continuous from the northern part of Africa through the Middle East to South-East Asia (Eberhardt *et al*, 2014). *T. evansi* transmission is not only different from that of the other African trypanosomes, but also its capacity to invade a host's tissues (such as *T. equiperdum*). The most pathogenic African livestock trypanosomes, *T. congolense* and *T. vivax***,** known as blood parasites, exhibit a direct relation between pathogenic effects and the presence of parasites in the blood. *T. evansi* can exhibit very high parasitaemia, especially in camels, horses, and dogs (and even occasionally cattle and buffaloes), and considered as both a blood and tissue parasite, due to its ability to invade the nervous system, not only in horses and dogs but also in cattle, buffaloes, and pigs (Holland *et al*, 2003). When the parasite is in very low numbers, can induce immuno-suppressive effects, or when it is absent from the host blood stream, although in the nervous system, identification of the etiological agent and evaluation of its pathogenic effects and impact are especially difficult. Thus, medical and economic impacts of *T. evansi* have been neglected. Amongst other things, this review aims to provide a new view on this old parasite whose tendency to travel does not appear to be extinct (Sengupta *et al*, 2012). The pathogenic effects of ***T.*** *evansi* are classical such as any other pathogenic mammal trypanosomes, including fever, anemia, loss of appetite and weight, loss of condition and productivity, nervous signs and/or abortion, cachexia, and death, with or without more peculiar signs related to the host species (Aref *et al*, 2013). However, what is quite surprising is the variable intensity of these signs, from totally unapparent to lethal, from one to another host species, but sometimes within a host species, depending on the geographical area or the epidemiological situation. Amongst nonvisible but very important effects of Surra is the immuno-suppression.

This is the first reported Egyptian human case of trypanosomiasis *evansi,* a neglected zoonosis and the 12th one worldwide (Otto *et al*, 2010). WHO (2005) described the first human case in the world caused by *T. evansi*. Joshi *et al.* (2006) treated the first reported human case of trypanosomiasis *evansi* by suramin. Powar *et al*. (2006) in India reported another zoonotic case.

Regarding Egyptian animal trypanosomiasis, El Sawally *et al*. (1998) found that Phenylpyruvic acid & 4-hydroxyphenylpyruvic acid were detected in urine of dogs and donkeys experimentally infected in Egypt with a recent field isolate of *T. b. evansi*. They added that the Tryptophan metabolites could not be assayed in dog and urine samples because formalin, which degraded the indole acids, had to be added before the samples could be imported into the U.S. They stated that the concentrations of urinary catabolites during infection were correlated with the tyrosine aminotransferase activity in infected mouse sera.

Hilali *et al*. (2004) used card agglutination test (CATT/*T. evansi*) to detect antibodies against *T. evansi* in experimentally and naturally infected buffaloes. The antibodies were detectable from day 8 PI till the end of the experiment. Parasitological examination of 200 water buffalo blood samples obtained from the slaughterhouses revealed negative results. The serological examination showed that 48 (24%) water buffaloes had anti-*T. evansi* antibodies. Hilali *et al*. (2006) studied the haematological and biochemical changes in the buffalo calves (*B. bubalis*) inoculated intravenously with camel isolate *T. evansi*. Liver function tests revealed significant elevation in the activity of LDH, globulin, total bilirubin and indirect bilirubin while alkaline phosphatase enzyme showed significant decrease. Kidney function tests revealed significant decrease of both the creatinine and urea. Saleh *et al*. (2009) estimated oxidation and antioxidant status in blood of camels' naturally infected with *T. evansi*, concluded that chronic *T. evansi* infection in camels was associated with a state of oxidative process.

Amer *et al.* (2011) assessed *T. evansi* in blood of dromedary camels (*C. dromedarius*) brought to Modern Al-Bassatein Abattoir, Cairo by mouse inoculation tested 484 camels found that 4.7% were infected. Besides, Elhaig *et al*. (2013) in Ismailia Governorate reported *T. evansi* in camels.

Apart from Egypt, Kaur *et al*. (2007) in India reported a case of trypanosomiasis caused by the rodent parasite *T. lewisi* in a two months old infant in urban Mumbai. Watier-Grillot (2008) in France reported an outbreak of animal *T. evansi* in the Aveyron department.

Generally speaking, *T. evansi*, the agent of "surra," is a salivarian trypanosome, originating from Africa. It is thought to derive from *T. brucei* by deletion of the maxicircle kinetoplastic DNA (genetic material required for cyclical development in tsetse flies). It is mostly mechanically transmitted by tabanids and *Stomoxys*, initially to camels, in sub-Saharan area. The disease spread from North Africa towards the Middle East, Turkey, India, up to 53° North in Russia, across all South-East Asia, down to Indonesia and the Philippines, and it was also introduced by the conquistadores into Latin America. It can affect a very large range of domestic and wild hosts including camelids, equines, cattle, buffaloes, sheep, goats, pigs, dogs and other carnivores, deer, gazelles, and elephants. It found a new large range of wild and domestic hosts in Latin America, including reservoirs (capybaras) and biological vectors (vampire bats). Bats were reported in all over Egypt (Ammar *et al*, 2003; Negm and Fakeer, 2014) with their zoonotic parasites (Rifaat *et al*, 1967) and arthropod vectors of diseases (Morsy *et al*, 1986). Surra is a major disease in camels, equines, and dogs, in which it can often be fatal in the absence of treatment, and exhibition of the nonspecific clinical signs (anemia, loss of weight, abortion, and death), which were variable from one host and one place to an-

other; however, its immunosuppressive effects interfering with the inter-current diseases or vaccination campaigns might be its most significant and questionable aspect. On the other hand, what is quite surprising is the variable intensity of these signs, from totally unapparent to lethal, from one to another host species, but sometimes within a host species, depending on geographical area or epidemiological situation. Amongst the non-visible but very important effects of surra is immunosuppression, which will be presented in the next section (Nguyen *et al*, 2014)

Nevertheless, *T. evansi* (Steel 1885) Balbiani, 1888, is the first pathogenic mammalian trypanosome to be described in the world, in 1880, by Griffith Evans, in the blood of Indian equines and dromedaries. Its principal host is originally the camel but it is present in dromedaries, horses, and other Equidae as well as in a large range of other hosts (Gardiner and Mahmoud, 1900). *T. evansi* is continuously present eastwards, in the Arabian Peninsula, including Oman, Saudi Arabia, the United Arab Emirates, as well as Jordan, Iraq, Israel, Lebanon, Syria, and Turkey, and even with occasional record in Bulgaria; it is present from Iran to Kazakhstan, Afghanistan and Pakistan (Hasan *et al*, 2006). Amoudi *et al*. (2011) in Saudi Arabia reported *T. evansi* in camels. Berlin *et al*. (2012) reported *T. evansi* in Israeli horses. Thompson *et al*. (2014) stated that of the exotic trypanosomes, *T. lewisi* is the only recorded from indigenous Australian mammals; morphological forms found in *Hydromys chrysogaster* and *Rattus fucipes.* Also, many Australian marsupial species were potentially at risk from the native chronically pathogenic *T. copemani*, while marsupials, rodents and monotremes were at risk to exotic *T. lewisi*, *T. cruzi* and *T. evansi*.

Conclusion

Atypical human infections caused by animals' trypanosomes other than human ones; the sleeping sickness due to *Trypanosoma b. gambiense* or *T. b. rhodesiense*, and Chagas disease due to *T. cruzi* were reported. These are *T. brucei brucei*, *T. vivax*, *T. congolense*, *T. evansi*, *T. lewisi*, and *T. lewisi*-like. Some *T. evansi*, infections were transient in nature, while the others required treatments.

No doubt, the presence of animal *T. evansi* in Egypt and the neighboring countries and the abundance of the insect-vector(s) and bats must be taken into consideration. This is true by detection of the first *T. evansi* zoonotic case. However, a number of cases of atypical human trypanosomiasis *evansi* might be underestimated.

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