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Review

Human African trypanosomiasis: a review of non-endemic cases in the past 20 years

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SUMMARY

Human African trypanosomiasis (HAT) is caused by sub-species of the parasitic protozoan *Trypanosoma brucei* and is transmitted by tsetse flies, both of which are endemic only to sub-Saharan Africa. Several cases have been reported in non-endemic areas, such as North America and Europe, due to travelers, expatriots or military personnel returning from abroad or due to immigrants from endemic areas. In this paper, non-endemic cases reported over the past 20 years are reviewed; a total of 68 cases are reported, 19 cases of *Trypanosoma brucei gambiense* HAT and 49 cases of *Trypanosoma brucei rhodesiense* HAT. Patients ranged in age from 19 months to 72 years and all but two patients survived. Physicians in non-endemic areas should be aware of the signs and symptoms of this disease, as well as methods of diagnosis and treatment, especially as travel to HAT endemic areas increases. We recommend extension of the current surveillance systems such as TropNetEurop and maintaining and promotion of existing reference centers of diagnostics and expertise. Important contact information is also included, should physicians require assistance in diagnosing or treating HAT.

1. Introduction

Human African trypanosomiasis (HAT), also known as sleeping sickness, is endemic to sub-Saharan Africa where it is a major threat to public health in 36 countries.[1] It is caused by *Trypanosoma brucei*, a single-celled eukaryotic parasite and member of the Kinetoplastida order.[2] Two subspecies are able to infect humans: *Trypanosoma brucei gambiense* causes a chronic form of HAT in West and Central Africa, while *Trypanosoma brucei rhodesiense* is the pathogenic agent for the more acute form of the disease and is endemic to Eastern Africa.[2,3] The parasite is transmitted by the bite of an infected tsetse fly (genus *Glossina*), and cases of HAT are only found in areas of tsetse fly infestation, which are limited to sub-Saharan Africa. However with the increased movement of people, some travelers, military personnel and immigrants have been reported as HAT-positive. Here, the non-endemic cases of HAT are reported, as well as their frequency and outcome; laboratory infections with *T. brucei* are considered outside the scope of this review.

The Trypanosoma parasites are transmitted through the bite of an infected tsetse fly,[4] and undergo complex changes during their life-cycle alternating between the insect vector and the mammal host. After the parasites are inoculated into man, they proliferate at the infection site, causing an inflammatory nodule or ulcer, also known as a trypanosomal chancre; it is typically described as a circumscribed, red, indurated nodule.[5] Previous studies have shown that the ulcer is much more commonly seen in patients suffering from *T. b. rhodesiense* HAT, with lesions in 70–90% of cases appearing 5–10 days after being bitten by the infected tsetse fly; this is around the same time as fever and detectable parasitemia in the blood.[6] Chancres are rarely seen in *T. b. gambiense* infections, possibly because most infections are detected after the chancre has disappeared.[7]

HAT can be classified into two clinical stages, depending on whether parasites have crossed the blood–brain barrier (BBB) into the central nervous system.[3] After inoculation, trypomastigotes spread via lymph into diverse peripheral tissues and organs initiating the hemolymphatic stage.[8] Diverse clinical symptoms, mostly reflecting inflammatory reactions, may appear, of which

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only fever and headache are common in all patients. Up to 50% of European patients develop a rash on the torso and most patients will have swollen, palpable lymph nodes.[9] Patients suffering from *T. b. gambiense* HAT will often show lymphadenopathy, usually on the back of the neck, a condition known as Winterbottom's sign. Parasites can, at this stage, be microscopically detected in blood and lymph node aspirates depending on parasite number.

Signs and symptoms may subside after the acute first stage. In the second stage, also known as the meningo-encephalitic stage, parasites enter the central nervous system.[8] This process occurs within weeks for *T. b. rhodesiense* or months or years after initial infection by *T. b. gambiense*. As the disease progresses, the classical signs of late-stage HAT become apparent:[8] severe headaches, a disruption of the circadian rhythm, with night-time insomnia and daytime somnolence; altered mental functions and personality changes may arise while generalized meningo-encephalitis can lead to coma and death.[4] Other symptoms including anorexia, altered endocrine functions,[10] demyelination and leuko-encephalitis are also typical.[11] It is important to note that not all patients will show the same signs and symptoms of HAT.

2. Diagnosis and treatment

Definitive diagnosis relies upon microscopy, however parasite numbers of less than 100 trypanosomes/ml can be difficult to detect with microscopy alone.[7] Concentration methods such as microhematocrit centrifugation,[12] quantitative buffy-coat analysis,[13] or mini-anion exchange columns[14] can be used to concentrate the parasites for easier microscopic detection. In West Africa, many endemic screening programs rely on the card-agglutination test for trypanosomiasis (CATT). The CATT is based on the antibody-mediated agglutination of fixed trypanosomes carrying particular surface glycoproteins and is a sensitive assay to detect *T. b. gambiense*-specific antibodies in blood.[15] *T. b. rhodesiense* lacks these particular surface glycoproteins and thus CATT is not appropriate for the diagnosis of *T. b. rhodesiense* HAT.[16] Patients with *T. b. gambiense* HAT are at risk of misdiagnosis with other infections due to cross-reacting antibodies against *Toxoplasma gondii*, *Strongyloides stercoralis*,[17] Epstein–Barr virus (EBV),[18] cytomegalovirus (CMV),[19] *Plasmodium fieldi*, *Plasmodium brasilianum*, and *Borrelia burgdorferi*.[20] Molecular techniques, such as polymerase chain reaction (PCR), loop-mediated amplification (LAMP) and nucleic acid sequence-based amplification (NASBA) have been developed and evaluated; however, they have yet to be adopted or validated for use in the clinical setting.[4,7,21–23]

To diagnose second-stage HAT, trypanosomes must be microscopically detected in the cerebrospinal fluid (CSF).[24] An elevated ($>5 \times 10^6$/l) number of white blood cells in the CSF is also used to define the second stage of the disease; however this cut-off is sometimes debated.[8]

There are only five licensed drugs for the treatment of HAT.[25] Pentamidine and suramin are available to treat the disease before parasites invade the central nervous system; pentamidine is the recommended drug in the treatment of first-stage *T. b. gambiense* HAT, and suramin is recommended for first-stage *T. b. rhodesiense* HAT.[8] To treat second-stage HAT, drugs that cross the BBB are essential.[4] Melarsoprol is the only drug available to treat *T. b. rhodesiense*-caused HAT and is the most economical,[26] while *T. b. gambiense* HAT can also be cured with eflornithine or a combination of eflornithine and nifurtimox.[27] Melarsoprol is an organo-arsenic compound that causes frequent adverse reactions, which can be severe and even life-threatening. While a comprehensive review on the treatment of HAT is available in Brun et al. 2010,[8] we have included some important contact information for assistance in the diagnosis and treatment at the end of this review.

3. Non-endemic clinical cases from the literature

A recent search of PubMed and ProMED-mail, as well as personal communication, resulted in 68 reported cases of HAT in non-endemic countries. Of these, 57 cases were found through a PubMed search (search terms: 'trypanosoma OR HAT OR African trypanosomiasis OR sleeping sickness NOT Chagas NOT animal NOT reservoir') and through a bibliographic search of articles. The search was limited to the past 20 years (1990–2010). Three cases, all related, were found by personal communication (P. Büscher).[28] A ProMED-mail search using 'trypanosomiasis' dating back to 1994 returned 184 reports, however there were only eight additional human cases. Many of these cases were also reported on TropNetEurop (http://www.tropnet.net/special_reports/tryps_ex_serengeti.pdf), a European surveillance network for imported infectious diseases.

4. Non-endemic West African trypanosomiasis

Nineteen cases of non-endemic *T. b. gambiense* HAT were found in the literature search (Table 1). Most of the cases were either immigrants (6/19, 32%) from endemic regions who had migrated to Europe, Australia or North America,[17,19,29,30] or ex-patriots (8/19, 42%) who had been stationed in endemic regions;[18,31–35] the remaining cases were unspecified (5/19, 26%). All described *T. b. gambiense* HAT cases were diagnosed after a considerable time had elapsed after the infection, which is typical for the chronic form.[8] Of the 19 cases of *T. b. gambiense* HAT, nine cases were diagnosed in the first stage of the disease, eight were diagnosed in the second, and two were not specified,[28] but all were successfully treated. Here we discuss selected cases that highlight important observations.

A New Zealand man had been posted in Nigeria and Gabon and was treated in the UK.[31] He was initially diagnosed with and treated for loa loa and schistosomiasis; however splenomegaly, lymphadenopathy, and elevated IgM levels persisted. Trypanosomiasis was suspected, but the positive diagnosis for HAT requires the detection of parasites. Initial examination of lymph, blood, and marrow failed to detect any parasites. Two months after his initial presentation, he returned and trypanosomes were detected in a blood smear and lymph node aspirates. These were presumed to be *T. b. gambiense* given the patient's history. He was treated and cured with suramin and difluoromethylornithine. Individually, these parasitic infections are rarely seen in non-endemic regions; for one patient to be diagnosed with all three seems "most improbable" (Scott, 1991).[31] It is important to remember that travelers to endemic regions may be exposed to many possible parasitic infections. Although one disease may be diagnosed, physicians should consider other possible infections, especially if atypical symptoms are present.

Three cases of *T. b. gambiense* HAT encountered in Portugal may be examples of unusual transmission of the disease.[28] A 30-year-old woman, who had never traveled to an endemic HAT region, was admitted to hospital in Portugal with lesions on her thighs, weakness, and pain. She was clinically and serologically diagnosed with Lyme disease. Fever, leukopenia, and anemia developed, which led to the microscopic examination of tissues, including CSF, where trypanosomes were detected. Both CATT and PCR were positive and indicated infection with *T. b. gambiense*. The patient was treated with eflornithine and was reported to be healthy 3 years later. While determining the route of transmission, it was discovered that her companion, a Brazilian man who had traveled to Angola for a military mission, was an asymptomatic carrier and he was subsequently treated. Sexual transmission was proposed, although sharing of needles during drug abuse cannot be excluded (P. Büscher, personal communication). Furthermore, the woman's