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Clinical management of East African trypanosomiasis in South Africa: Lessons learned

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ABSTRACT

Background: East African trypanosomiasis is an uncommon, potentially lethal disease if not diagnosed and treated in a timely manner. South Africa, as a centre for emergency medical evacuations from much of sub-Saharan Africa, receives a high proportion of these patients, mostly tourists and expatriate residents.
Methods: The cases of East African trypanosomiasis patients evacuated to South Africa, for whom diagnostic and clinical management advice was provided over the years 2004–2018, were reviewed, using the authors' own records and those of collaborating clinicians.
Results: Twenty-one cases were identified. These originated in Zambia, Malawi, Zimbabwe, Tanzania, and Uganda. Nineteen cases (90%) had stage 1 (haemolymphatic) disease; one of these patients had fatal myocarditis. Of the two patients with stage 2 (meningoencephalitic) disease, one died of melarsoprol encephalopathy. Common problems were delayed diagnosis, erroneous assessment of severity, and limited access to treatment.
Conclusions: The key to early diagnosis is recognition of the triad of geographic exposure, tsetse fly bites, and trypanosomal chancre, plus good microscopy. Elements for successful management are rapid access to specific drug treatment, skilled intensive care, and good laboratory facilities. Clinical experience and the local stock of antitrypanosomal drugs from the World Health Organization have improved the chance of a successful outcome in the management of East African trypanosomiasis in South Africa; the survival rate over the period was 90.5%.

Introduction

Human African trypanosomiasis comprises two vector-borne protozoan diseases with morphologically indistinguishable pathogens but different epidemiological and clinical features. Both forms of the disease are transmitted by blood-feeding dipteran flies, but the vector and pathogen species, geographical range, and reservoir host types are unique to each. Rhodesiense or East African trypanosomiasis (EAT) is caused by the zoonotic flagellate *Trypanosoma brucei rhodesiense*, transmitted by tsetse flies of the *Glossina morsitans* (savannah species) group, whereas gambiense or West African trypanosomiasis (WAT) results from infections from the largely anthroponotic *Trypanosoma brucei gambiense*, with vectors belonging to the *Glossina palpalis* (riverine tsetse species) group; *Glossina fuscipes*, a member of this group, transmits both EAT and WAT. Geographically, the historic extent of the Great Rift Valley separates the distributions of the two diseases; only Uganda has both forms, but they occur in different areas (Franco et al., 2014; World Health Organization, 2017b).

From a public health perspective, human African trypanosomiasis is regarded by the World Health Organization (WHO) as a neglected tropical disease, falling into a subset that is designated 'endemic or neglected zoonotic diseases', together with bovine tuberculosis, anthrax, cysticercosis, rabies, brucellosis, leishmaniasis, and hydatidosis. These diseases occur at the convergence of poverty, high reliance on animals (wild or domestic) for livelihoods, and close contact between humans and animals (Mableson et al., 2014).

Since 1997, the WHO and partners have greatly improved both access to trypanosomiasis treatment and control measures in

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endemic areas, particularly for WAT (Franco et al., 2014; Simarro et al., 2011). From 1998 to 2016, annual WAT cases dropped from 37 000 to 2131, across 24 countries. EAT cases dropped from 1933 in 1990 to the current annual average of around 100 cases (53 in 2016), in 13 countries (Simarro et al., 2010; World Health Organization, 2017a). WAT may in future be completely eliminated, but this will not be possible for EAT because of its zoonotic nature; however, its elimination as a public health problem may be feasible, by applying multisectoral One Health principles (Franco et al., 2014; World Health Organization, 2017b).

Previously, access to antitrypanosomal drugs for EAT, i.e. suramin (Bayer Pharma) and melarsoprol (Sanofi), was limited in non-disease-endemic countries. Presently the drugs are donated to the WHO and distributed through its Unit of Innovative and Intensified Management in the Department of Control of Neglected Tropical Diseases (Simarro et al., 2011). By agreement with the WHO, a hospital pharmacy repository for the drugs that allows 24-hour access has been established in Johannesburg, and in consultation with the National Institute for Communicable Diseases, they are supplied free of charge locally on request. (Other institutions stocking the drugs are listed in Büscher et al., 2017.)

Travellers and migrants, having been infected in endemic areas, may present with an unfamiliar disease that challenges the diagnostic and clinical management skills of healthcare providers in non-endemic countries (Simarro et al., 2012). This article highlights the problems that East African trypanosomiasis patients have presented when referred to South African medical facilities and the important lessons that have been learned in the process of managing them.

Patients and methods

South Africa does not have endemic trypanosomiasis, but it is a travel hub for tourists and migrants, and for medical evacuation flights serving much of Sub-Saharan Africa. The National Institute for Communicable Diseases in Johannesburg provides diagnostic and clinical advice for trypanosomiasis cases evacuated to South Africa. A review was performed of the available reports on those patients with whom the National Institute for Communicable Diseases was directly involved from 2004 to 2018 (and therefore a subset of all cases reported from South Africa (Simarro et al., 2012)). Information on the laboratory diagnosis and clinical management of these patients was extracted in order to provide practical insights for the management of such patients in the future. Original references are given for cases reported previously, mainly in monthly surveillance summaries produced by the National Institute for Communicable Diseases.

Most patients were transported as formal medical evacuees from the area where they became ill and were referred with either a confirmed diagnosis or for investigation of non-malaria fever. With few exceptions, they were admitted to private hospitals in Johannesburg and Pretoria. On laboratory confirmation of the diagnosis by microscopic examination of Giemsa-stained blood films, suramin treatment was given according to published recommendations (Abdi et al., 1995). A test dose solution (200 mg of suramin diluted in 2 ml of sterile water) was given intravenously, first as a few microlitres, followed by 1 ml, then the remainder, with a 1-min observation period for any adverse reactions between doses. The suramin treatment regimen was 5 mg/kg by slow intravenous infusion on day 1, 10 mg/kg on day 3, and then 20 mg/kg on days 5, 11, 17, 23, and 30, to a maximum cumulative dose of 10 g. Biochemical evidence for nephrotoxicity was monitored during and after the course of treatment. Once the parasites had been cleared from the peripheral blood (usually soon after the first treatment dose) and the patient's general condition had improved sufficiently, a lumbar puncture was done and the cerebrospinal fluid (CSF) was assessed immediately for direct (presence of trypanosomes) and indirect (cell count, protein concentration) evidence of central nervous system (CNS) involvement. Two patients required further treatment for stage 2 (meningoencephalitic) infection with melarsoprol, as follows: 2 mg/kg intravenously daily for 3 days, three times at weekly intervals, combined with prednisolone 60 mg daily.

Results and discussion

Since 2004, the present authors have assisted with the diagnosis and management of 21 EAT cases acquired in five African countries. Patient demographics, risk factors, stage of disease, and key clinical features and outcomes are summarized in Table 1. Seven patients acquired the infection in Zambia and six in Malawi; three cases originated in Tanzania, three in Zimbabwe, and two in Uganda (Figure 1). Most were tourists (13/21, 62%) and the remainder (8/21, 38%) had occupation-related exposure (game ranching or conservation, military, business, or commercial tourism). In many cases, full clinical and laboratory information was not available.

There was a preponderance of males (17/21, 81%), as has been noted previously for EAT (Duggan and Hutchinson, 1966; Franco et al., 2014). There were no indigenous African patients in this series, which was inherently biased towards health-insured tourists. Two cases were Zambian nationals of South Asian descent. Ethnicity-related differences in clinical presentation have previously been noted (Duggan and Hutchinson, 1966), infection in non-Africans generally being more acute.

Although this series of cases is widely heterogeneous in terms of geographic exposure and clinical and laboratory features at presentation, certain problems tended to recur in the areas of initial clinical assessment, laboratory investigation, and treatment. Specific examples relate to cases listed in Table 1.

Lack of awareness of trypanosomiasis and persistence with ineffective treatment

Most patients gave a history of painful tsetse fly bites, but the presence of trypanosomal chancres was often ignored or overlooked in the initial clinical assessment, or they were commonly misinterpreted as insect, spider, or tick bites, or as bacterial cellulitis (cases 8–10, 13, 14, 21). Uninfected tsetse fly bites produce a local skin reaction, sometimes quite marked, but this subsides rapidly. At the time of clinical presentation, the typical chancre is a distinct area of moderate subcutaneous swelling, about 3–5 cm in diameter, firm and slightly tender on palpation, with marked erythema (and later, increased pigmentation) and some desquamation or superficial ulceration of the overlying skin, but usually without overt necrosis; however, there is considerable variation in appearance, as shown in Figure 2. A distinctive circinate skin rash is said to occur in up to one third of patients (Büscher et al., 2017), but was not apparent in any of the cases in this series. One patient developed an antibiotic-associated rash, initially ascribed to a suramin reaction (Figure 2E). One patient had a subacute presentation resembling gambiense trypanosomiasis (case 1, Table 1), with a history of several months of deteriorating mental function, but was subsequently proven to be infected with *T. b. rhodesiense* (Checkley et al., 2007).

Chancres are not invariably present; of the most recent 15 patients, two (cases 17 and 18) did not have them. In some endemic countries, local or expatriate doctors may not be aware of the disease because it is so rare in comparison with other causes of fever, like malaria (cases 4, 12, 13, 19, 21). There is a wide differential diagnosis for the early signs and symptoms of EAT,