

Sleeping Sickness: Cause and Control

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ABSTRACT

Sleeping sickness (Human African Trypanosomiasis) is a complex and debilitating disease afflicting the marginalized communities in Sub-Saharan Africa. The disease is one of the most neglected diseases in terms of knowledge of the disease, drug development and control resulting to its persistence despite decades of attempt at vector and chemotherapeutic control. Sleeping sickness is caused by parasitic Protozoa of the genus *Trypanosoma* and is transmitted by bites of infected tsetse fly. The human infective species include *Trypanosoma brucei gambiense* and *T. brucei rhodesiense* which do not differ morphologically from *T. brucei* which cause similar disease described as “Nagana” in animals. Two forms of the disease are recognized. The chronic form described as Gambian trypanosomiasis caused by *T. brucei gambiense* is endemic in West and Central Africa and poses difficulty in diagnosis due to typically low parasitaemia. The acute form, Rhodesian trypanosomiasis caused by *T. brucei rhodesiense* is endemic in East Africa and parts of Central Africa. Both forms of disease are zoonotic in natural and occur in two clinical stages. The early or haematolyphatic stage is characterized by symptoms that are observed before central nervous system involvement. Control of sleeping sickness is dependent on accurate diagnosis, vector control, and effective chemotherapeutic management of patients. So a treatment for early stage involves the use of pentamidine and suramin. However, in the late stage, the use of melarsoprol and Eflornithine as a treatment pair proves most effective. Presenting obstacles to effective control of sleeping sickness include insufficient surveillance, encephalopathy of arsenic compounds and implicating roles of animal reservoir hosts. Prospects for future control is therefore dependent on development of new drugs, workable national control programs, improved diagnostic tools and adopting integrated control approach which incorporates trypanosomiasis control in animals.

Keywords: aetiology, clinical features, Human African Trypanosomiasis, treatment prospects

Abbreviations: CATT, Card Agglutination test for Trypanosomiasis; CNS, Central Nervous System; CSF, Cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HAT, human African trypanosomiasis; IF, Immuno fluorescence; IHA, indirect haemagglutination; ISCTRC, International Scientific Council for Trypanosomiasis Research and Control; PATTEC, Pan-African Tse tse and Trypanosomiasis eradication campaign; PCV, packed cell volume; PCR, Polymerase Chain reaction; SIT, Sterile Insect Technique; VSG, Variant Surface glycoprotein

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INTRODUCTION

Human African Trypanosomiasis (HAT) also known as sleeping sickness is a complex and debilitation disease afflicting the marginalized communities in sub-Saharan Africa. The disease has over the years been recognized as one of Africa’s most persistent and deadly scourges causing depopulation and underdevelopment (Jordan 1986; Hursey

2000). The pathology had been discovered since the beginning of the 20th century (Bruce and Nabarro 1903) and was known to slave traders in West Africa (Nash 1969). Since then sleeping sickness has passed through several phases characterized by undulating epidemics, different disease control campaign strategies and research towards understating the pathogenesis of African trypanosomes and drug control. Sleeping sickness has today been listed among the

most neglected diseases (Morel 2003; Truc 2003). The neglect of sleeping sickness in terms of knowledge of the disease, drug development and control has resulted to its persistence despite decades of attempt at vector and chemotherapeutic control. The last decade witnessed the resurgence of the disease where it now poses as a public health hazard in endemic countries and increasing reports of infection among tourists returning from tropical Africa (Conway-Klaassen *et al.* 2002; Jelinek *et al.* 2002). HAT poses a major problem in Angola, Democratic Republic of Congo and Sudan while most of the old endemic foci in endemic countries including Nigeria remains active (Abenga *et al.* 2004; Jennin 2004). Although over 200 endemic foci exist in 36 countries (Anon 1998; Jennin 2005) the present status of the disease is not well known and probably underestimated. The pan-African Tse Tse and Trypanosomiasis Eradication Campaign of the African Union set up in 2000 which emphasizes disease control through vector eradication using appropriate methods especially the Sterile Insect Technique (SIT) (Kabayo 2004) though expensive promises to be one of the most successful initiatives by member states for the control of the disease on the continent.

This review summarizes the ethiological as well as clinical features of HAT and assesses the current strategies in the control of the disease and the role of intergrated approach in winning the war against sleeping sickness.

CAUSATIVE ORGANISMS

Sleeping sickness is caused by a parasitic protozoan of the genus *Trypanosoma* and sub-Genus Trypanozoon (Lumsden 1974). The human infective species include *Trypanosoma brucei gambiense* and *T. brucei rhodesiense* which do not differ morphologically from *T. brucei brucei* which causes a similar disease in animals described as “Nagana” (Jordan 1986). All members of this sub-Genus are also typically pleomorphic with sub-terminal kinetoplast. Characterization of Trypanozoon stocks based on simple biological methods such as the Blood-Incubation – Infectivity test (Richman and Robson 1970) and the more sophisticated biochemical and molecular procedures such as iso-enzyme, chromosome and DNA analyses and protein mapping (Gibson *et al.* 1978; Anon 1998) are useful tools in differentiating members of this subgenus and their distribution (Hide and Tait 2004). Antigenic variation, a phenomenon whereby blood stream trypanosomes switch from one variant surface glycoprotein (VSG) to another constitute a major set back to drug control and development of Vaccine against the disease (Donelson 2003; Barry and Carrington 2004).

RESERVOIR HOSTS

Hitherto, the role of animal reservoir in the transmission of HAT was believed to be more important in *T.b. rhodesiense* than *T.b. gambiense* (Anon 1998), however recent evidences based on molecular and other biotechnologies suggest that animal reservoir hosts play roles in transmission and current resurgence in *T.b. gambiense* HAT in sub-Saharan African (Abenga and Lawal 2005). Pigs have been identified as important reservoirs of *T.b. gambiense* and have been associated with persistence of disease in Uganda (Abenga and Lawal 2005), Equatorial Guinea (Simarro *et al.* 2001), Cameroon (Nkinin *et al.* 2002) and Nigeria (Onah and Ebenebe 2003). Wild ungulates on the other hand have been identified as important reservoirs of *T.b. rhodesiense* which makes *T.b. rhodesiense* infection occupation associated, the high risk groups being honey gatherers, hunters, fishermen, fuel wood collectors and lately tourists (Conway-Klaassen *et al.* 2002; Jelinek *et al.* 2002).

GEOGRAPHICAL DISTRIBUTION

HAT exists in sub-Saharan African between latitudes 14°N and 29°S within the geographical distribution of human infective trypanosome and their tsetse vector.

Two forms of HAT are recognized which differ both in distribution and disease course (Welburn *et al.* 2004). The devastating and chronic form described as Gambian trypanosomiasis and caused by *T.b. gambiense* exists in West and Central Africa and poses special problem in diagnosis due to typically low parasitaemia (Anon 1998; Lejon *et al.* 2003). The acute form, Rhodesian trypanosomiasis caused by *T.b. rhodesiense* on the other hand exists in East and Central Africa in which case both forms of the disease occur in the Central African sub-region (Anon 1998). However, *T.b. gambiense* sub species described as Type I and Type II may exhibit different types of disease. Where as Type I organism present classical *T.b. gambiense* disease characterized by low virulence, Type II produces an acute rhodesiense-like disease course (Anon 1998). The current situation in endemic countries indicates that the prevalence of the disease differs from one country to another as well as in different parts of a single country. Major outbreaks have been observed in Angola, the Democratic Republic of Congo and Sudan. In Central African Republic, Chad, Congo, Ivory Coast, Guinea, Malawi, Uganda and Tanzania sleeping sickness remains an important public health problem. In countries such as Burkina Faso, Cameroon, Equatorial Guinea, Gabon, Kenyan, Mozambique, Nigeria, Rwanda, Zambia and Zimbabwe fewer than 50 new cases are being reported (Dargie 2007).

TRANSMISSION

HAT is principally transmitted by bites of an infected tsetse fly (*Glossina*) especially *Glossina palpalis* and *G. tachinoides* even though other species also have capacity for cyclical transmission of the parasites (Scott 1970; Rogers and Robinson 2004).

CLINICAL FEATURES

Two phases of clinical HAT are recognized, the early or stage I and the late or stage II phases (Poltera 1985; Anon 1998). Both forms of sleeping sickness are diseases of central nervous system CNS and other tissues with an initial period of infection of the blood by infected tsetse fly following later by invasion of the CNS. The time course of disease varies with the type of infecting trypanosome species.

The early, stage I or haematolymphatic stage is characterized by symptoms that occur before CNS invasion by trypanosomes, the early sign of infection being the development of a chancre, an inflammatory skin nodule at the site of tsetse bite accompanied later by periodic fever, headache, joint pains, muscle aches, pruritis and later cachexia. Lymphadenopathy characterized by palpable firm, mobile enlargement of lymph glands occurs especially in the neck region. There may also be generalized oedema especially of the face described as “moon face” (Jordan 1986) which may extend also to the appendages. There is moderate anaemia as well as endocrinological disorders which result in disturbances in reproduction such as reduced libido, impotence, abortion and infertility (Anon 1998). Abnormalities in electro-cardiogram in patients, is also reported.

The late stage or meningoencephalic stage sets in following CNS involvement and may be established by the demonstration trypanosomes (Poltera 1985), or raised immunoglobulin M level (Chappuis *et al.* 2005) in the CSF. The onset of this stage may also be accompanied by demonstration of urinary nitrites and nitrate which follow closely brain nitric oxide associated with penetration of trypanosome in the brain, and occurrence of the sleep-onset rapid eye movement like episodes (Jannin and Cattand 2004). This stage is characterized by disturbances of the CNS and manifests as deep hyperaesthesia, paraesthesia, convulsions, mental disorders, insomnia, somnolence, ataxia, paresis and paralysis (Jordan 1986; Anon 1998). In the typical Gambian trypanosomiasis, invasion of the CNS is delayed and death of untreated victims may not occur for several years and the patient emaciates over several months also displaying typi-

cal sleeping syndromes (Jordan 1986). In animal models, the time duration for onset of CNS signs vary from one animal species to another. In our recent observations in vervet monkeys experimentally infected with *T.b gambiense*, the CNS signs occurred at the eighth week and death at the 15th week post infection while there was a relationship between CNS pathology, PCV and weight loss in late stage disease (Abenga and Anosa 2004, 2005, 2006, 2007). In *T.b. rhodesiense* infection however, earlier death of patients may occur within few weeks or months of infection without CNS involvement (Anon 1998).

CONTROL STRATEGIES

Diagnosis

Prompt diagnosis and staging of HAT is essential for chemotherapy of the disease. Diagnosis of HAT relies on an initial serologic screening with the CATT followed by parasitologic confirmation in endemic areas (Anon 1998; Chappuis *et al.* 2004; Lejon and Buscher 2005). For practical and logistic reasons, techniques such as immunofluorescence (IF), indirect haemagglutination (IHA), enzyme-linked immunosorbent assay (ELISA) and DNA techniques based on polymerase chain reaction (PCR) are most suitable for use in the laboratory than in the field. The body fluids used for confirmatory parasitological diagnosis includes blood, lymph node aspirates and cerebrospinal fluid (CSF) and where necessary bone marrow aspirates and ascites fluids (Anon 1998). Since the second stage of sleeping sickness is associated with risk of severe complications, detection of parasite in the blood and lymph node aspirates should be followed by CSF examination to determine the stage of the disease.

Chemotherapy

Drug control of HAT is still dependent largely on drugs developed before 1950 (Anon 1998; Boutielle *et al.* 2003; Moore 2005; Schmid *et al.* 2005). Drugs for the early stage treatment include Pentamidine and Suramin compounds while melarsoprol and eflornithine are generally drugs of choice for the late stage. For melarsoprol, a highly toxic arsenical with 2-12% incidence of fatal side effects (Boutielle *et al.* 2003) its use can be improved by shortening the regime. The International Scientific Council for Trypanosomiasis Research and Control (ISCTRC) recommended the shorter protocol for treatment of late stage *T.b. gambiense* (Schmid *et al.* 2005). Major obstacles to effective chemotherapy of sleeping sickness include unacceptable toxicity, poor efficacy, undesirable route of administration and drug resistance (Fairlamb 2003; Nok 2003).

Vector control

Tse tse control based on insecticides, targets, and traps with use of baits remain some of the important principles of the control of *Glossina*, vectors of sleeping sickness (Vale and Torr 2004; Lee 2005). The large scale tse tse control on the continent of Africa through the PATTEC initiative by member states of the African Union has prospects for cooperative control of the vector (Kabayo 2004). Control based on research results on molecular and genomic aspect of tse tse in identifying tse tse genes that may be used as tools to disrupt trypanosome growth and spread of such genes in tse tse population has been proposed (Lee 2005).

Veterinary component

Although this aspect of HAT control has not received much attention over the years, recent molecular evidences confirmed several animal reservoir hosts for *T.b. gambiense* and their roles in resurgence of the disease (Nkinin *et al.* 2002; Onah and Ebenebe 2003; Abenga and Lawal 2005). Control of trypanozoon infections in animals holds prospect as a

tool in breaking the animal – tse tse – man transmission cycle.

CONCLUSION

HAT has a reputation of being one of the deadly scourges that has plagued Africa for more than a century. Prospects for success in the war against the disease is dependent on intergration of approaches and surmounting of the present control obstacles which includes inadequate resources, inadequate surveillance, inadequate knowledge of the disease, lack of effective diagnosis, adverse reaction and cost of drugs, absence of new drugs, human population movements, and agro-ecological changes that alter tsetse habitats and increase contact between humans and tsetse flies. Resurgence of the disease in the face of collapse of tsetse fly belts in some endemic areas suggests an imperative need for a search light on alternative transmission methods and re-evaluation of the sleeping sickness risk groups which are likely to differ from one community to another.

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USEFUL RELATED WEBSITES

- http://en.wikipedia.org/wiki/Sleeping_sickness
- <http://www.emedicine.com/med/topic2140.htm>
- <http://www.doctorswithoutborders.org/news/sleepingsickness/index.cfm>
- <http://www.nlm.nih.gov/medlineplus/ency/article/001362.htm>
- <http://www.who.int/mediacentre/factsheets/fs259/en/>
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