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Review

Translation of human African trypanosomiasis biomarkers towards field application

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ABSTRACT

Sleeping sickness is a neglected tropical disease affecting rural communities in sub-Saharan Africa. The reduction in the number of reported cases in recent years indicates that disease transmission is under control. However, many aspects of patient management still need to be improved. Undiagnosed patients or inappropriate treatment due to an incorrect determination of the disease stage could in fact lead to its re-emergence. There is thus a strong need for new diagnostic and staging tools to keep the disease under control and to improve the clinical care of patients. This review describes the most promising biomarkers proposed so far for the diagnosis and stage determination of patients suffering from sleeping sickness, with a particular emphasis on their translation into diagnostic tools for field applications.

Contents

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1. Introduction

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a neglected tropical disease endemic in sub-Saharan Africa, mainly affecting rural communities [1]. It is a focal disease caused by an extracellular protozoa belonging to the *Trypanosoma* genus. After infection, parasites proliferate in blood and lymph, giving rise to the first stage (S1) of the disease. In the absence of treatment, it evolves into the second stage (S2) due to parasite invasion of the central nervous system (CNS). Even though the number of newly reported cases of HAT in 2009 was approximately 10,000, the real number is estimated to be three times higher [2]. In most cases, sleeping sickness is fatal if untreated. Transmission of the disease is currently considered to be under control and it may even be heading towards eradication [3], however, due to the lack of vaccines and prophylaxis, great efforts will be needed to maintain the status quo or even improve the current situation. Patient management is still not considered optimal, with numerous cases missed at diagnosis or not correctly staged and treated. This review aims to summarize the most interesting findings in terms of novel biomarkers and tools proposed so far to improve the management of patients affected by human African trypanosomiasis.

2. Human African trypanosomiasis (HAT): epidemiological and clinical aspects

Sleeping sickness is endemic in 200 known foci in 36 countries in sub-Saharan Africa [4] and the associated disease burden was estimated at 1,609,041 DALYs lost in 2004 [5,6]. Two subspecies of *Trypanosoma brucei* parasites are responsible for the disease: *T. b. gambiense* and *T. b. rhodesiense*. These forms are resistant to the trypanosome lytic factor present in human blood, whereas other species such as *T. b. brucei*, *T. vivax* and *T. congolense*, are sensitive to it [7,8]. The Serum Resistance Associated (SRA) gene, coding for the SRA protein, has been identified as the resistance factor in *T. b. rhodesiense* [9,10], while *T. b. gambiense*'s resistance mechanism is still unknown. Both parasites are transmitted to humans by tsetse flies of the *Glossina* genus, and undergo a cyclic transmission between the vector and the human host [1,2]. Importantly, the geographical distribution of the tsetse fly in sub-Saharan Africa determines the location of the disease within the so-called tsetse belt [2].

T. b. gambiense is responsible for chronic infection in 24 countries in western and central Africa, accounting for more than 90% of all reported HAT cases. *T. b. rhodesiense* causes acute infection in eastern Africa and is responsible for less than 10% of reported cases [3,11]. The two forms of parasite are geographically separated by a line across Uganda [12].

Historically, disease prevalence followed in waves of epidemics mainly linked to the socio-political instability of the affected countries. The resolutions adopted by the WHO and NGOs during the 1990s led to a consistent reduction in the number of reported cases, quantified by decreases of 69% for the *gambiense* form and 21% for the *rhodesiense* form, during the period 1997–2006 [3]. Currently, disease transmission is considered to be under control, with 19 of the 36 endemic countries registering no new cases in 2009 [11].

Sleeping sickness progresses through two stages. The first stage (stage 1, S1), or haemolymphatic stage, occurs after an incubation period that can vary from 1 to 3 weeks after the bite of the tsetse fly. This stage is characterized by the proliferation of parasites in the bloodstream and the lymphatic system. If S1 patients are not properly treated, the disease progresses to the second stage (stage 2, S2) or meningo-encephalitic stage, when parasites invade the CNS [13]. The disease is considered to be fatal if untreated [14]. The speed of progression from S1 to S2 varies according to the infecting parasite: for *T. b. gambiense*, S1 can last for months or years before evolving into S2, while the evolution of *T. b. rhodesiense* HAT from S1 to S2 occurs within a few weeks of infection [14].

In both forms of HAT, early stage patients present unspecific clinical symptoms and signs [15]. Stage 1 disease can often mimic other illnesses endemic in the same regions, such as malaria and HIV, which can even coexist in patients affected by sleeping sickness [16].

As the disease evolves into S2, the clinical symptoms and signs become more specific, with the appearance of neurological disorders of different types as a consequence of meningo-encephalitis, including impaired motor functions, tremors, psychiatric changes and coma [14]. The clinical manifestations of the two forms of HAT are different and, generally, *T. b. gambiense* patients present more evident neurological disorders [15]. A characteristic neurological complication of sleeping sickness, which gives the disease its name, is a dysfunction of the sleep-wake cycle, with daytime sleepiness and alterations of the normal sleep patterns with the appearance of sleep onset REM periods (SOREMPs) [17].

The diagnostic workflow for HAT patients consists of three phases. The first phase, the serological screening, consists in mass population examination using the Card Agglutination Test for Trypanosomiasis (CATT) to identify patients potentially affected by *T. b. gambiense*. In all positive patients,