Clinical and biological evolution of human trypanosomiasis in Côte d'Ivoire

Despite more than 60 years of control activities, human African trypanosomiasis (HAT) remains an important health problem in sub-Saharan Africa. In 1998, for example, the World Health Organization estimated that 60 million were at risk of acquiring the disease and that as many as 500,000 people were infected with *Trypanosoma brucei* spp., the causative agents (WHO, 1998). Two stages of the disease are classically observed: a haemato-lymphatic stage, in which there are no specific clinical signs (Jannin *et al.*, 1993; Dumas and Bouteille, 1996), leading to a meningo–encephalitic stage, usually characterized by neurological disorders. However, human infection with *T. b. gambiense*—the cause of the usually chronic form of HAT (often known as Gambian sleeping sickness) found in West and Central Africa—may be asymptomatic (Gallais *et al.*, 1953; Lapeyssonnie, 1960; Wery and Burke, 1972; Ginoux and Frézil, 1981; Woodruff *et al.*, 1982) or even cause acute disease, as suspected in Côte d'Ivoire (Truc *et al.*, 1997). This diversity in clinical pattern may reflect variation in the parasite, in individual susceptibility to infection, or both. However, the relationship between the genetic diversity of *Trypanosoma brucei* spp. and the clinical evolution of HAT is still a matter of controversy, and marked variation in the susceptibility of humans to infection has never been demonstrated.

In Côte d'Ivoire, 63 people living in the Sinfra area (30 local-born and 33 migrants from Mali, Burkina Faso or northern Côte d'Ivoire) refused treatment for 1–5 years after they had first been found infected with trypanosomes in 1995–1996. Whenever possible and appropriate (see below), each was clinically re-examined and re-checked for infection with *T. b. gambiense* at regular intervals during this period (June 1997, January 1998 and March 1999). Plasma samples were checked with the card agglutination test for trypanosomiasis (CATT; Magnus *et al.*, 1978), whole blood was investigated using the miniature anion-exchange centrifugation technique (mAECT; Lumsden *et al.*, 1977), and lymph-juice samples (from those with swollen lymph nodes) were checked under the microscope, for trypanosomes. Although the main aim of these investigations was to persuade those infected to accept appropriate treatment, the results obtained are of considerable interest and are therefore reported here.

By the time of the first follow-up, in June 1997, two of the subjects had died (of unknown causes) and 11 had left the Sinfra area, leaving 53 available for re-examination. By the time of the last follow-up, in March 1999, 29 of these 53 had accepted treatment and two more subjects had died, both with severe neuro–psychiatric illness probably attributable to HAT. Only 19 of the original subjects had died, both with severe neuro–psychiatric illness probably attributable to HAT. Only 19 of the original subjects were therefore left untreated and available for the final follow-up. Two of these refused to permit blood samples to be taken from them in March 1999 (although clinical examination of these two at each of the three follow-ups failed to reveal any signs of HAT) and blood samples were not taken from another two subjects at this last follow-up because they had been found to be CATT-negative at the first follow-up, in 1997. The serological, parasitological and clinical data discussed below are confined to the 15 subjects, here numbered 1–15 for convenience, who were still untreated at the last follow-up and from whom blood samples were taken at that time (see Table).

Numbers 1–8 were all parasitologically negative at the 3-year follow-up, although either CATT-positive in 1999 (numbers 3–8), or CATT-positive in 1997 and 1998 and CATT-negative in 1999 (numbers 1 and 2). Numbers 1–6 had never been found to have...
any signs indicative of HAT during the follow-up period, although number 5 had had several clinical signs characteristic of the second-stage of the disease (i.e. sleepiness, sexual impotence and behavioural disorders) when first examined in 1995. Numbers 7 and 8, who were only available for the March 1999 follow-up, where then found to have some of the clinical manifestations of HAT. [When first examined, in 1996, number 7 had impaired consciousness, behavioural disorders and trypanosomes in his cerebro-spinal fluid (CSF).]

Although numbers 9–14 where found to be positive for infection, both parasitologically and by the CATT, in March 1999 and whenever checked during the follow-up period, only one of these six subjects, number 14, was ever seen with a neuro-psychiatric disorder (and then only at the final follow-up).

The final subject to be considered, number 15, was CATT-positive and parasitologically positive in June 1997 and January 1998 but negative, both by the CATT and the mAECT, at the last follow-up in March 1999. During the follow-up period of the present study, this subject was also examined by staff from the Daloa-based Projet de Recherche Contre la Trypanosomiase (PRCT), in November 1998 and January 1999. On both of these occasions, subject 15 was found negative by the CATT and the mAECT and no trypanosomes could be found in CSF samples. Thus this subject was apparently CATT-negative from November 1998 to the end of the present study.
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That 63 trypanosome-infected subjects refused treatment for months or even years is disconcerting. Such subjects may simply have wondered why they needed treatment when they felt well (the first stage of HAT being largely asymptomatic), being unaware of how their infection might develop into lethal disease if left untreated. Fortunately, follow-up visits convinced 29 of these subjects to accept treatment, although sometimes only after neurological disorders had developed (data not shown).

The seroconversion, from CATT-positivity to CATT-negativity, seen among some of the subjects who remained asymptomatic throughout the follow-up period (e.g. numbers 1, 2 and 15), is unusual. Subjects 1 and 2, who were never found trypanosome-positive after first being found infected in 1995–1996, may have had infections with T. congolense (Truc et al., 1998) or T. b. brucei rather than T. b. gambiense. Although T. congolense and T. b. brucei are human-serum sensitive and probably quickly eliminated, transient infections with these parasites may induce a non-specific immune response and lead to false-positive CATT results because of cross-reactivity (Noireau et al., 1986). However, the slow seroconversion observed in subjects 1 and 2 is inconsistent with a transient infection with a non-human parasite, since such infections are unlikely to maintain CATT positivity for 2 or 3 years.

Trypanosomes isolated from subject 15, who had become CATT-negative by November 1998, were confirmed to be of T. b. gambiense group 1 (Gibson, 1986) by multilocus enzyme electrophoresis (MLEE; Jamonneau et al., 2000). Thus, subjects 1, 2, and 15 were probably infected with T. b. gambiense when first examined in 1995–1996, and probably became CATT-negative by March 1999 as the result of clearance of their infections, even though they had not been treated with ‘conventional’ medicine. These three cases were therefore probably examples of self-cure, although some of the present subjects (3, 5 and 15) were followed-up and probably partially treated by a ‘healer’. The efficacy of traditional medicines used to treat HAT remains unclear and must be investigated.

The present data confirm that HAT is diverse in its clinical evolution, with infections that remain asymptomatic (Gallais et al., 1953; Ginoux and Frézil, 1981) and some apparent cases of self-cure as well as those that lead into the second-stage of the disease, with chronic or acute neurological disorders. This variation may be associated with genetic variability in the parasites, as observed in Uganda (Smith and Bailey, 1997). However, the genetic variability of trypanosome stocks from Côte d’Ivoire, mostly collected in the Sinfra area, has always appeared to be very low, whether investigated using the repetitive sequences of microsatellite DNA and PCR (Biteau et al., 2000), RAPD or MLEE (Jamonneau et al., 2000). The results of MLEE (Jamonneau et al., 2000) have, in fact, indicated that the parasites infecting subjects 9–15 in the present study belonged to the same zymodeme, and no relationship between zymodeme and pathogenicity in humans has ever been noticed in studies in Côte d’Ivoire.

Is variation in human response to the infection, rather than variation in the parasite, responsible for the diversity in clinical evolution? Ginoux and Frézil (1981) suspected that asymptomatic infection, with low parasitaemia, no swollen lymph nodes and no neurological sign, was the result of human trypanotolerance. Such a phenomenon may explain why subjects 3–8 in the present study remained CATT-positive but apparently aparasitaemic (Kabiri et al., 1999). Although the trypanotolerant individual may remain asymptomatic for several years, the equilibrium may be broken, leading to the sudden appearance of nervous disorders, as observed in other trypanotolerant animals (Murray et al., 1990; Authié, 1994). Variation in individual susceptibility to infection has been already demonstrated for both viral (Michael et al., 1997) and bacterial infections (Altare et al., 1998) and the results of numerous studies indicate that host genetics play a role in susceptibility to infection with some parasites (Marquet et al., 1996; Garcia et al., 1999). In mice, genes on chromosomes 5, 11 and 17 of the host are involved in resistance to T. congolense (Kemp
et al., 1997), and indirect data indicate a similar link in human infection with T. b. rhodesiense (Okia et al., 1994). In Central Africa, the trypanolytic activity of sera from Bantus is markedly different to that of sera from Pygmies (Authié et al., 1991). Further investigation is needed to see if ethnicity (and therefore genetics) affects susceptibility to HAT, in the same way that it affects susceptibility to leishmaniasis (Alcais et al., 1997).

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V. JAMONNEAU
A. GARCIA
Unité de Recherche et de Lutte contre la THA,
Institut Pierre Richet,
B.P. 1500, Bouaké 01,
Côte d’Ivoire, and Département Sociétés et Santé,
Institut de Recherche pour le Développement (IRD-ex ORSTOM),
911 Avenue Agropolis,
34032 Montpellier, France

J. L. FRÉZIL
Département Sociétés et Santé,
Institut de Recherche pour le Développement (IRD-ex ORSTOM),
911 Avenue Agropolis,
34032 Montpellier, France

P. N’GUSSAN
L. N’DRI
R. SANON
Unité de Recherche et de Lutte contre la THA,
Institut Pierre Richet, B.P. 1500,
Bouaké 01, Côte d’Ivoire

C. LAVESSIÈRE
Département Sociétés et Santé,
Institut de Recherche pour le Développement (IRD-ex ORSTOM),
911 Avenue Agropolis, 34032 Montpellier,
France, and Laboratoire de Recherche sur les Trypanosomatidés, OCEAC,
B.P. 288, Yaoundé, Cameroon

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