Host age and time of exposure in *Trypanosoma brucei* gambiense Human African Trypanosomiasis

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**Summary**

Human African Trypanosomiasis is related to behavioural risk factors but complex interactions exist between (i) environmental and behavioural risk factors, (ii) vector and (iii) human host. Our aim was to investigate the interrelationships between previously analysed risk factors and the roles of age and time of exposure according to ethnic group and migration status. However, this descriptive and retrospective study is based on cases only (no controls) and our results must therefore be regarded as hypothesis-generating. Individuals originating from areas where sleeping sickness is absent and who settle in an endemic area seem to develop the disease after a shorter time of exposure than native subjects from endemic areas. Our results emphasise the complexity of vector-transmitted disease epidemiology, involving behavioural and/or environmental risk factors on the one hand, and more individual ones such as ageing, immunity and genetic background on the other hand.

**keywords** Human African Trypanosomiasis, epidemiology, risk factors

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**Introduction**

Sleeping sickness or Human African Trypanosomiasis (HAT) is an important health problem in sub-Saharan Africa, responsible for a high degree of suffering and mortality, especially in rural populations living in forest zones (coffee and cocoa plantations) who are regularly exposed to vector bites (i.e. glossina or tsetse fly). Analysis of the localization and frequency of human-fly contact shows that infection with human trypanosomiasis is related to behavioural risk factors (Laveissière et al. 1986a, b; Médéa et al. 1993). However, Moore et al. (1999) recently underlined the complex interactions existing between (i) environmental and behavioural risk factors, (ii) presence of the vector and (iii) the human host, as the prevalence of the disease seems not to be correlated with the apparent density of tsetse flies (Sané et al. 1999).

Behaviour associated with forest activities is strongly related to both age and ethnic group (Laveissière et al. 1986b). The importance of age as risk factor for the disease seems also to depend on the epidemiological situation, and although sleeping sickness appears more often in adults than children (Frézil et al. 1981; Moore et al. 1999), this difference varies according to prevalence levels (Jannin et al. 1992). Differences in disease prevalence according to ethnic group are a consequence of each group’s distinctive pattern of agricultural activity and way of life, which modifies the level of human-fly contact (Laveissière et al. 1994a; Sane et al. 1999). Age-related differences between ethnic groups have not been explored to our knowledge. The complex effect of age as a measure of both the duration of exposure to infectious agents, and the duration of development of immunity has been investigated in other parasitic diseases, such as malaria (Baird 1995), in which involvement of genetic factors is strongly suspected (Garcia et al. 1998). In leishmaniasis the effects of ageing can be different between natives from endemic areas and migrants, depending on the age at migration into the area (Alcaïs et al. 1997).

Our aim was to describe the respective roles of age and time of exposure according to ethnic groups and migration status. As this study was retrospective and based only on
data from cases (no controls), the contribution of ethnicity or migration status cannot be regarded as risk factors, but it serves to generate hypotheses on the origins of observed differences between groups.

**Materials and methods**

**Study area and population**

The study took place in the Western-Central part of Côte d’Ivoire in Sinfra HAT focus. The ombrophilic forest has mostly disappeared and coffee and cocoa plantations prevail. Several ethnic groups are present in the area, consisting of autochtonous (Gouro) or allochtonous tribes from other areas of Côte d’Ivoire (mainly Baoule), and several groups from northern areas of Côte d’Ivoire, Mali or Burkina Faso, denoted as Sudanese people and consisting mainly in Senoufo and Mossi. Sudanese people use a collective system of land occupancy and mix with the local population, whereas autochtonous groups mostly live in villages and are without farms; their plantations are among those of Sudanese people or are cultivated by them. Conversely, the Baoule live more individually, mixing less with other people.

**Case detection and recorded variables**

Active case detection organized by the Pierre Richet Institute and health authorities from 1992 to 1997 discovered 679 sleeping sickness cases in Sinfra focus. The programme involved a family census of more than 50 000 individuals, who were registered by community health agents. For each individual living in the area, age and gender were recorded. The involvemnt of community health agents convinced communities to strongly participate in active HAT case detection in repeated mass screenings performed as part of this control programme.

In 1999, our team visited each of the cases still present in the area to record (1) gender; (2) age in years; (3) age at diagnosis in years; (4) year people settled in the area; (5) ethnic group, classified as originating from northern areas with absence of disease or extremely low level of endemicity (northern Côte d’Ivoire, Burkina Faso, Mali) or from other areas where HAT is or has been present, and denoted as southern ethnic groups; and (6) migration status, classified as born in the area (native) or coming from other areas (migrant). Each area of transit before arriving in Sinfra focus was recorded, but most migrants went from their birthplace to Sinfra.

For each group, i.e. migrant vs. native; northern vs. southern ethnic group, a mean age of diagnosis (MAD) was classically computed. However, the MAD did not reflect the period of exposure to HAT risk for migrants as this period began when people settled down in the area. To take this point into account a new variable, denoted as exposure period (EP), was defined for migrants as: age at diagnosis minus age at settling in the area. For each group of migrants a mean exposure period (MEP) was computed to perform analyses. For natives, the exposure period corresponds to the age at diagnosis (MAD = MEP). In further analyses MEP was used to study the effect of migration on the age at diagnosis in this population.

The population was composed of 485 sleeping sickness cases for whom information concerning both the diagnosis of the disease and the individual variables was confirmed. To ensure maximum reliability, a comparison was made between our case registration and that of the local treatment centres. After the purpose of the study had been explained, informed consent was obtained from the study subjects.

**Statistical analysis**

Univariate analyses were performed to study the relationship between age at diagnosis and recorded variables, by means of one-way analysis of variance (ANOVA). Multivariate analysis was conducted by means of multiway ANOVA. Bonferroni t-tests and Student-Newman-Keuls multiple range tests were used for multiple comparisons. As age was not normally distributed, a log-transformation was used prior to analyses. Moreover, equality of variances was tested prior to ANOVA, by means of Levene’s test. All computations used BMDP statistical software (University of California, Los Angeles, CA, USA).

**Results**

**Description of the population**

The mean age of the population was 32.3 years [standard error of mean (SEM) = 0.81] with a sex-ratio, male/female, of 1.2. Fifty-nine per cent of the population belonged to northern ethnic groups and the remaining 41% were from ethnic groups from southern areas. Apart from ethnic groups, 63.7% of the population were natives of Sinfra focus. However, among subjects belonging to northern ethnic groups, 47% were born in Sinfra area, whereas this rate was 85% for individuals from southern ethnic groups.

**Migration status and ethnic group effect**

The MAD was 27.5 years (SEM = 0.80) in the whole population apart from migration status. Taking into
account exposure period for migrants the MEP in the whole population was 19.9 years (0.43).

Mean age at diagnosis differed significantly \((P < 10^{-4})\) between natives and migrants, 22.2 years (1.03) and 36.8 years (1.02), respectively. Considering exposure period for migrants, the difference remained significant \((P < 10^{-4})\), but reversed: MEP was 15.9 years (0.79) for migrants and 22.2 years (1.03) for natives (Figure 1).

Apart from migration status, MAD was significantly lower \((P < 0.004)\) for cases from northern ethnic groups than for the other, 25.3 years (0.93) and 31.6 years (1.40), respectively. Taking into account migration status by considering only cases born in Sinfra focus, this difference remained significant \((P < 10^{-4})\); 13.2 years (0.65) for northern ethnic groups and 29.1 years (1.53) for southern ethnic groups (Figure 2).

An ethnic group may be considered as a confounding variable as 83% of migrants belong to northern ethnic groups \((P < 10^{-4})\). A multivariate analysis was then performed using both ethnic group and migration status as

![Figure 1](image1)

**Figure 1** Relative frequencies of sleeping sickness cases according to migration status; age at diagnosis (natives) vs. exposure period (migrants).

![Figure 2](image2)

**Figure 2** Relative frequencies of sleeping sickness cases for individuals born in Sinfra focus.
explicative variables for onset of sleeping sickness. Whereas ethnic group remained strongly significant ($P < 10^{-3}$), migration status became borderline significant ($P = 0.049$) and an interaction between the two variables was significant ($P = 0.001$), meaning that the effect of migration differed according to ethnic group. The interpretation of this interaction remained difficult as one of the two explicative variables (migration status) was borderline significant. To deal with this result we performed multiple comparisons using Bonferroni t-tests and the Student–Newman–Keuls multiple range test. Both of these procedures led to the same results (Table 1). Age of diagnosis was significantly higher for individuals belonging to the southern ethnic group born in the area (group 1 in Table 1) than for both northern ethnic group native to the area (group 3) ($P < 10^{-3}$) and northern ethnic group migrant (group 4) ($P < 10^{-3}$). No effect of migration ($P > 0.2$) was observed within northern ethnic group cases (group 3 vs. group 4). Nevertheless, the effect of migration within southern ethnic group individuals (group 1 vs. group 2) did not reach Bonferroni significance level ($P < 0.06$) although only 28 cases belong to group 2. This group is composed of Baoule individuals originating from the centre of Côte d’Ivoire, from a very degraded forest area border on the Western-Central HAT focus of Côte d’Ivoire.

Discussion

Our main result is that age at diagnosis has to be considered as a complex variable. Considering age at diagnosis alone, individuals originating from areas where sleeping sickness is absent and who settle down in endemic area seem to develop the disease later than subjects born in endemic areas. However, taking into account that migration is also a time-dependent variable, previous results are reversed, consistent with the fact that people coming from non-endemic areas could develop the disease after a shorter period of exposition at risk. Our results suggest that although the ethnic group is an important risk factor for sleeping sickness (Laveissière et al. 1986b), migration status has also to be taken into account and underlines the possible interaction between them. Even though migration has no effect for individuals belonging to northern ethnic groups it might be an additional risk factor for subjects from other ethnic groups from areas where sleeping sickness is nowadays absent, in a still active focus. The borderline non-significant result might be because of the lack of power of analysis related to the low number of migrant individuals from southern ethnic groups.

To assess the role of ethnic group or migration status as risk factors we should compute the variations of the instantaneous risk of HAT with age for each group. Instantaneous risk can be correctly approximated by incidence rates for each age group but the information allowing to compute incidence rates for migrants (i.e. migration date) was not available for the whole population living in the area. In Sinfra focus this would concern more than 50 000 individuals, most of them being there illegally. However, our goal was only to describe the effect of age in each ethnic group and to generate hypothesis concerning the reasons why ethnic groups are considered as a risk factor.

Control activities in Sinfra, which involved health care workers from all the villages of the area, censused the whole population. Medical surveys covered 75% during the first 4 months (WHO 1998). After this first medical screening, several active surveys were conducted and the Sinfra trypanosomiasis laboratory was equipped to perform both serological and parasitological diagnosis as daily routine. All these elements are consistent with the fact that Sinfra focus was extensively described and the great majority of the population was medically examined at least once during the control programme, suggesting that age at diagnosis might be considered, in the present study, as a good approximation of age of onset, or at least that the same average delay may be applied to the whole population independently of both their ethnic group or migration status. As an illustration, we performed a medical survey in October 1999 in the three villages with the worst epidemiological situation at the beginning of the control activities (the prevalence reached 4% in one of them), and the overall prevalence during this survey was 0.2%.

In all endemic foci of the forest area of Côte d’Ivoire, the allochthonous people from northern areas such as Mali,
Burkina Faso and northern Côte d’Ivoire with very low prevalence or absence of HAT are the principal victims of the disease (Laveissière et al. 1994a). In the Vavoua focus (Western central part of Côte d’Ivoire), the prevalence among the Mossi (originating from Burkina Faso) was 6.1% whereas it was only 0.6% among the Baoule (Laveissière et al. 1994b). This difference was presented as a consequence of agricultural activities and way of life between the two groups, the Mossi being much more in contact with tsetse flies. Our observation that individuals from northern ethnic groups develop the disease more rapidly when settled in a transmission area, is consistent with this assumption. Daily activities have been frequently described as important risk factors for HAT in forest areas responsible not only for higher prevalence rates (Laveissière et al. 1986a; Moore et al. 1999) but also for both spatial and familial cases clustering (Henry 1981; Khonde et al. 1997). Khonde et al. (1997) showed that the risk of HAT in children was correlated to a history of HAT in the mother but not in the father. This result could be because of the fact that children, during the first 2 years of life, spend a lot of time with their mother, exposed to tsetse bite when collecting water.

However, another explanation could be that people from areas where the disease is absent are more susceptible to infection that individuals originating from endemic areas. One interesting epidemiologic feature of sleeping sickness is that the epidemics of the 1970s and 1980s appeared in areas where the disease is absent are more susceptible to infection early during exposure, but the difference between forest and northern groups seems to decrease rapidly in young adults (Figure 2). The same pattern occurs in other parasitic diseases for which the involvement of individual susceptibility has been demonstrated (Alcaïs et al. 1997). The interaction between potential genetic factors and age has been described for malaria (Garcia et al. 1998), and there are arguments for the existence of such an individual susceptibility in Trypanosoma brucei gambiense infection (Garcia et al. 2000; Jamonneau et al. 2000). New studies exploring the role of genetic factors are now ongoing for human African trypanosomiasis.

Finally, our results underline the complexity of vector-transmitted diseases’ epidemiology, involving behavioural and/or environmental risk factors on the one hand, and more individual ones (such as ageing, immunity and genetic background) on the other hand. It seems very important to develop an overall vision taking into account not only previous risk factors separately but also their complex interactions in order to generate hypotheses on the way these risk factors affect exposed individuals.

Acknowledgements

We are deeply grateful to Alexis Zohoury and all primary health care workers from the Sinfra control programme for technical assistance in the field. This study received financial support from the Ministère français des Affaires Etrangères (Direction du Développement et de la Coopération technique, Fonds d’Aide à la Coopération); Institut de Recherche pour le Développement (IRD – ORSTOM).

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