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Use of symptoms and signs for diagnosis of *Trypanosoma brucei rhodesiense* trypanosomiasis by rural health personnel

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The results are described of a study of 60 patients with sleeping sickness from north-east Zambia together with 60 hospital controls and 27 nearest-neighbour controls. Eight symptoms were significantly commoner among sleeping-sickness patients than among either set of controls, and some of these symptoms were used to devise a scoring system for use by rural medical personnel. Although most patients reported a short history of the illness, almost 90% had abnormal cerebrospinal fluid, and there was a significant tendency for the cerebrospinal fluid of adults with a longer history of sleeping sickness to contain trypanosomes. Enlargement of lymph nodes was significantly more frequent among the patients than among the controls, but often the submandibular, axillary, or inguinal rather than the posterior cervical nodes were enlarged. Signs associated with involvement of the central nervous system were common, but the cheiro-oral reflex was non-specific, also occurring frequently among hospital controls.

In areas where the prevalence of endemic rhodesiense sleeping sickness is low, the disease tends to occur sporadically among widely scattered rural populations who live within or visit the tsetse-fly belts. When symptoms develop, these patients first go to isolated rural health centres where the auxiliary medical personnel have to differentiate between them and large numbers of other patients with fever or other complaints. Sophisticated diagnostic tests are very rarely available in such centres, but it is very important that all patients who are likely to have trypanosomiasis should be identified and referred at an early stage for proper management. Diagnosis of trypanosomiasis before involvement of the central nervous system has occurred greatly reduces the adverse reactions to treatment. Also, effective surveillance and early treatment with drugs decrease considerably the risks of human transmission and epidemic spread of the disease (*1*, *2*).

In the present study we compared the symptoms and signs exhibited by trypanosomiasis patients with those of suitable controls in order to develop a simple scoring system for use by rural health workers in making an initial presumptive diagnosis of the disease. We also attempted to clarify whether some signs generally held to be diagnostic criteria are specific for trypanosomiasis. The study was carried out from May 1981 to December 1982 in the northern Luangwa valley, in north-east Zambia. Patients came from 57 villages located in an area of approximately 5000 km^2, whose population was about 10 000.

MATERIALS AND METHODS

Patients with sleeping sickness were defined as individuals from whom trypanosomes were detected, either during a survey by medical assistants in Isoka and Chama districts or after admission to one of three hospitals in the Northern and Copperbelt provinces. Two age- and sex-matched controls were identified for each patient: one from the same hospital and the other a nearest neighbour of the patient (*3*). Patients and controls answered the same questionnaire about their activities and were examined physically using a standard format. The questionnaire was in two parts. The first dealt with specific symptoms and provided for any additional symptoms (see Table 5). The second, concerning the physical examination, was directed at specific areas

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Table 1. Age and sex distributions of the 60 patients with sleeping sickness in the survey

Age group (years)	No. of patients		
	Male	Female	Total
0–4	1 (1.7)[a]	1 (1.7)	2 (3.3)
5–9	0	5 (8.3)	5 (8.3)
10–14	1 (1.7)	0	1 (1.7)
15–19	4 (6.7)	3 (5.0)	7 (11.7)
20–39	13 (21.7)	7 (11.7)	20 (33.3)
40–59	17 (28.3)	6 (10.0)	23 (38.3)
⩾60	2 (3.3)	0	2 (3.3)
Total	38 (63.3)	22 (36.7)	60 (100)

[a] Figures in parentheses are percentages.

Table 2. Distribution of symptoms among the 60 patients with sleeping sickness in the survey

Symptom	No. of patients with the symptom		
	Volunteered[a]	After examination[b]	Total
Headache	38 (63.3)[c]	6 (10.0)	44 (73.3)
General body pain	26 (43.3)	20 (33.3)	46 (76.7)
Fever	24 (40.0)	19 (31.7)	43 (71.7)
Malaise	19 (31.7)	19 (31.7)	38 (63.3)
Joint pains	18 (30.0)	21 (35.0)	39 (65.0)
Excessive daytime sleeping	15 (25.0)	23 (38.3)	38 (63.3)
Swelling of legs	14 (23.3)	12 (20.0)	26 (43.3)
Itching	10 (16.7)	11 (18.3)	21 (35.0)
Diarrhoea	9 (15.0)	5 (8.3)	14 (23.3)
Cough	6 (10.0)	8 (13.3)	14 (23.3)
Nocturnal sleeplessness	5 (8.3)	12 (20.0)	17 (28.3)
Swelling of face	4 (6.7)	9 (15.0)	13 (21.7)
Chancre	1 (1.7)	2 (3.3)	3 (5.0)

[a] Symptom admitted spontaneously by patient.

[b] Symptom admitted by patient only after being specifically asked.

[c] Figures in parentheses are percentages.

or systems of the body and patients were examined following a set order. Responses from patients and controls were obtained through the same interpreter under as similar conditions as possible. Hospital controls were selected by taking the first hospital inpatient found who was of the same sex and age group as the patient. The results of the physical examinations are described here, while the analysis of the responses to the questionnaire appear elsewhere (*3*).

The clinical examination protocol asked patients to describe their specific symptoms and their duration before admission to hospital. Specific physical signs alleged to be characteristic of trypanosomiasis were also sought (*2*, *4–7*). Blood was taken for thick films to exclude trypanosomiasis among the controls. Samples of cerebrospinal fluid were also analysed: involvement of the central nervous system was defined as either the presence of trypanosomes or of a raised leukocyte count ($>5 \times 10^9$ per litre cerebrospinal fluid) together with protein levels of >25 mg per 100 ml cerebrospinal fluid (*2*).

Data were recorded on pre-coded forms and analysed with the help of a computer.[a] Results for patients and controls were compared using McNemar's χ^2-test and the paired t-test.

RESULTS

One hundred and eight patients with sleeping sickness were identified. They were examined at various stages of their illness, in many cases after they had already been hospitalized for some considerable time; however, only those patients who had been examined within 2 weeks of admission to hospital were included in the survey.[b] The 60 patients who formed the basis of the survey were matched with hospital controls, while 27 patients were also matched with nearest-neighbour controls (Table 1).

Symptoms

The symptoms exhibited by patients are shown in Table 2, while the duration of the commoner symptoms is shown in Table 3; it is worth noting that case histories were usually short. The results of analysis of cerebrospinal fluid are shown in Table 4, together with the duration of symptoms before admission. Data for children under 10 years of age are shown separately since a higher proportion (66.7%) had trypanosomes in their cerebrospinal

[a] Hewlett Packard 9845B.

[b] Patients with sleeping sickness admitted to hospital are not usually given specific therapy until an improvement in their general condition has been sustained for 1–2 weeks following treatment for malaria and usually after blood transfusions.

Table 3. Duration of most frequent symptoms of patients before admission to hospital

Symptom	No. of patients, by duration of symptom		
	1–7 days	8–14 days	>14 days
Headache	22 (50.0)[a]	9 (20.5)	13 (29.5)
General body pain	18 (39.1)	12 (26.1)	16 (34.8)
Fever	22 (51.2)	9 (20.9)	12 (27.9)
Malaise	18 (47.4)	9 (23.7)	11 (28.9)
Joint pains	20 (51.3)	5 (12.8)	14 (35.9)
Excessive daytime sleeping	21 (55.3)	3 (7.9)	14 (36.8)
Swelling of legs	13 (50.0)	6 (23.1)	7 (26.9)
Itching	10 (47.6)	6 (28.6)	5 (23.8)

[a] Figures in parentheses are percentages.

fluid than did older patients (39.2%) and because accounts of their symptoms were probably less reliable. Data for two adults whose sleeping sickness recurred within 1 year of previous treatment are omitted from Table 4: the cerebrospinal fluid of one was normal but trypanosomes were detected in that of the other. Also, for one child the result of the analysis of the cerebrospinal fluid was not available. The cerebrospinal fluid of patients older than 10 years of age was significantly more likely ($\chi^2 = 7.5$, 2 degrees of freedom, $P < 0.05$) to contain trypanosomes the longer these patients had experienced the symptoms of trypanosomiasis.

Comparison of cases and controls. Table 5 shows the results of a discordant-pair analysis of patients with hospital and neighbour controls. Headache, general body pain, fever, malaise, joint pain, excessive daytime sleeping, swelling of legs, and itching were significantly more frequent among patients than in either of the control groups. Nocturnal sleeplessness and swelling of the face were also significantly more frequent among patients than in neighbour controls but not hospital controls; also, coughing was significantly more frequent among hospital controls than patients.

Past history of trypanosomiasis. Eight patients (13.3%) had a past history of admission to hospital with sleeping sickness. Two of these had received treatment within one year of the present survey and may well have relapsed; two others had been treated less than 2 years previously; and the remaining four at various periods between 2 and 9 years previously.

Table 4. Observed changes in the cerebrospinal fluid of patients and duration of symptoms before admission to hospital

Cerebrospinal fluid	Duration of symptoms			
	⩾2 days	3–7 days	⩾8 days	Total
Patients over 10 years of age				
Normal	1	2	0	3
Raised protein level[a]	6	3	1	10
Raised white cell count[b]	0	2	0	2
Raised protein and white cells	9	6	1	16
Trypanosomes and raised protein	3	0	1	4
Trypanosomes, raised protein and cells	2	8	6	16
Total	21	21	9	51
Patients under 10 years of age				
Raised protein level[a]	1	0	0	1
Raised white cell count[b]	0	1	0	1
Trypanosomes, raised protein and cells	3	1	0	4
Total	4	2	0	6

[a] Protein level of >25 mg per 100 ml cerebrospinal fluid.

[b] White cell count of $>5 \times 10^9$ cells per litre cerebrospinal fluid.

Table 5. Discordant-pair analysis of symptoms from 60 patients/hospital controls and 27 patients/neighbour controls

Symptom	No. of subjects with the symptom			
	Patients	Hospital controls	Patients	Neighbour controls
Headache	24	3[a]	12	0[b]
General body pain	32	5[a]	16	2[b]
Fever	22	7[a]	15	2[b]
Malaise	23	9[c]	15	2[b]
Joint pains	25	9[c]	18	1[a]
Excessive daytime sleeping	26	0[a]	18	2[a]
Swelling of legs	20	3[a]	9	0[c]
Itching	18	5[c]	10	1[c]
Diarrhoea	13	19	5	1
Cough	7	18[d]	7	2
Nocturnal sleeplessness	16	8	10	1[c]
Swelling of face	12	4	6	0[d]

[a] $P<0.001$.
[b] $P<0.005$.
[c] $P<0.025$.
[d] $P<0.05$.

Physical signs

The temperature of patients and controls measured orally did not differ significantly, although only one reading was taken at the time of interview.

Lymph node enlargement. The distribution of enlarged nodes indicates that for patients with rhodesiense sleeping sickness, practically any of the superficial lymph nodes may be enlarged.[c] Since in Africa slight enlargement of the inguinal nodes is extremely common and nonspecific in communities that are predominantly agricultural, we defined as significantly enlarged only the inguinal nodes of diameter $\geqslant 2$ cm and other lymph nodes if their diameter was $\geqslant 1$ cm. The distribution of the diameters of the largest palpable node in patients and controls is shown in Table 6, which indicates that 59% of patients had at least one enlarged lymph node compared with 22% of hospital and 17% of nearest-neighbour controls.

Hepatomegaly. No significant difference was observed between the proportion of patients and controls with enlarged livers.

Splenomegaly. Splenic enlargement was significantly more common among patients than among hospital controls, and the proportion of patients with enlarged spleens was greater than that of neighbour controls, but was not statistically significant (see Table 7). Forty-three per cent of patients had palpable spleens.

Cardiovascular system. The mean pulse rate of patients (95.0 ± 19.3 beats per minute) was significantly greater than that of either set of controls (hospital, 88.5 ± 17.6; neighbour, 83.2 ± 14.5). Also, for patients the mean diastolic blood pressure (68.5 ± 9.7 mmHg) was significantly lower ($P<0.05$; paired t-test) than that of the nearest-neighbour controls (75.7 ± 12.11 mmHg); however, in this respect there was no significant difference between patients and hospital controls. It should, nevertheless, be noted that the procedures used to measure blood pressures in the village and hospital environments may have differed.

Central nervous system. Twenty-eight patients (47%) had altered deep tendon reflexes, 86% of these being excessively brisk and the remaining 14% greatly reduced or absent. Tremor of the fingers was exhibited by 25% of patients and the same proportion

[c] The distribution of enlarged lymph nodes among the 60 patients was as follows: submandibular 26 (43.3%), cervical 25 (41.7%), epitrochlear 6 (10%), axillary 30 (50%), inguinal 55 (91.7%), and popliteal 10 (16.7%).

Table 6. Location and diameter of enlarged lymph nodes among patients

Diameter (cm)/ location of lymph nodes	No. of subjects		
	Patients	Hospital controls	Neighbour controls
None enlarged	2 (3.3)[a]	10 (16.9)	6 (25.0)
0.1–0.9/General 0.1–1.9/Inguinal	22 (36.7)	36 (61.0)	14 (58.3)
1.0–1.9/General 2.0–2.9/Inguinal	31 (51.7)	11 (18.6)	4 (16.7)
>2.0/General >3.0/Inguinal	5 (8.3)	2 (3.4)	0 (0.0)
Total	60 (100)	59 (100)[b]	24 (100)[c]

[a] Figures in parentheses are percentages.
[b] One hospital control refused to have axillary lymph nodes measured.
[c] Two neighbour controls refused to have any lymph nodes measured, and one refused to have inguinal nodes measured.

Table 7. Discordant-pair analysis of physical signs from 60 patients/hospital controls and 27 patients/neighbour controls

Physical sign	No. of subjects with the sign			
	Patients	Hospital controls	Patients	Neighbour controls
"Significantly" enlarged lymph nodes	27	4[a]	14	1[b]
Splenomegaly	22	8[c]	7	2
Impaired memory	8	0[c]	4	0
Tremor	14	2[c]	8	1[d]
Abnormal reflexes	20	7[c]	12	0[b]

[a] $P<0.001$.
[b] $P<0.005$.
[c] $P<0.025$.
[d] $P<0.05$.

Table 8. Scoring system for the preliminary diagnosis of sleeping sickness based on patients' symptoms

Symptom	No. of points, by duration of symptoms		
	<1 week	⩾1 week	Any period
Headache	1	2	–
Fever	1	2	–
Swollen legs	–	–	2
Itching	–	–	2
General body pain	–	–	1
Daytime sleepiness	–	–	1
Maximum score: 10			

Table 9. Distribution of scores of patients and controls

Score	Number of:		
	Patients	Hospital controls	Neighbour controls
0	2	17	16
1	2	11	2
2	1	9	4
3	2	12	4
4	9	6	0
5	10	4	0
6	8	1	0
7	12	0	1
8	12	0	0
9	1	0	0
10	1	0	0
Total	60	60	27

had an abnormal gait. Impairment of mental orientation was observed in 18% of patients while 14% had impaired memory. Tremor and abnormal reflexes were significantly more frequent among patients than among either set of controls, while impaired memory was significantly more frequent among patients than hospital controls (Table 7). The hand-chin or cheiro-oral reflex was elicited in 11 patients (18.3%), but also in 8 hospital controls (13.3%), a difference that is not significant.

Diagnostic scoring system

On the basis of the symptoms exhibited by patients, we devised a scoring system that may be a useful aid to auxiliary medical personnel in rural areas in making a preliminary diagnosis of sleeping sickness. Details of the system are outlined in Table 8, while the scores of patients and controls are shown in Table 9. If a score of ⩾4 out of 10 is taken as indicating trypanosomiasis, the method has a sensitivity of 88.3% and specificity of 81.7% compared to hospital controls. Use of physical signs instead of symptoms as the basis for the method was less successful, while use of both symptoms and signs did not improve the sensitivity or specificity.

DISCUSSION

The initial symptoms of trypanosomiasis are non-specific, and a survey in Chibale area of the northern Luangwa Valley at the beginning of the 1981 dry season found that over half the population had experienced headache in the previous 2 weeks and nearly half had had fever. Daytime sleepiness and symptoms associated with damage to the central nervous system are much less common in the general population than in those with trypanosomiasis (*8*). In rural areas it is difficult for auxiliary medical personnel to identify patients with sleeping sickness from the large numbers with malaria and other short-term fevers, and very often diagnosis has to be made without the aid of blood films or other laboratory tests. The simple scoring system described here may be useful in this respect, and we propose to evaluate it prospectively in rural areas.

The majority of patients in the study claimed to have been admitted to hospital within 2 weeks of the onset of symptoms, but only 3 out of 57 (5.3%) samples of cerebrospinal fluid analysed were normal. Children under 10 years of age seem particularly prone to early involvement of the central nervous system, with four of the six children in the study having detectable levels of trypanosomes in their cerebrospinal fluid. It is likely that many patients have only intermittent and rather vague symptoms

for some time after infection, as illustrated by the example of a 9-year old girl in this series who had trypanosomes in her blood, but whose parents refused to take her to hospital, despite repeated advice to the contrary. She remained only intermittently febrile and her condition remained stable for 4 months before she was eventually admitted for treatment.

Relapses of sleeping sickness were fairly frequent (13%) in the study sample. Unfortunately it was difficult to distinguish between relapse and reinfection, since some patients had not received optimal treatment because, *inter alia*, they prematurely discharged themselves from hospital. It is clear, however, that rhodesiense sleeping sickness does not confer complete immunity against reinfection.

The frequency of some physical signs of sleeping sickness was probably underestimated in this study, since some patients had already been hospitalized for up to 14 days before assessment. Enlargement of lymph nodes was common in patients, a finding that is inconsistent with some reports of rhodesiense sleeping sickness (*9*, *10*). The most frequently enlarged nodes were the submandibular, axillary, or inguinal rather than the posterior cervical nodes observed with gambiense sleeping sickness (Winterbottom's sign), and this is consistent with findings reported elsewhere (*4*). Splenomegaly was significantly more frequent among patients than hospital controls, but, in an area where malaria and infection with *Schistosoma mansoni* abound, splenic enlargement probably results from a variety of causes. The frequency of peripheral edema was probably higher among sleeping sickness patients than that observed in this survey, where it did not differ significantly from that of hospital controls; however, this may be due to the edema disappearing during the first few days in hospital, since many patients reported a history of swelling of the legs before being taken into care.

Of all the changes in the central nervous system, tremor of the fingers, impaired memory, and altered deep tendon reflexes were the most important. There is a subjective element in the elicitation of deep reflexes, which makes the interpretation of very brisk reflexes difficult; however, many of the patients had sustained patellar or ankle clonus. It has been reported that patients with sleeping sickness tend to develop brisk reflexes during the early stages of central nervous system involvement and that the reflexes return to normal or become sluggish as the infection progresses (*6*). The hand-chin reflex appeared to be non-specific, since it was also exhibited by 13% of hospital controls with various diagnoses.

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RÉSUMÉ

SYMPTÔMES ET SIGNES DES TRYPANOSOMIASES À *TRYPANOSOMA BRUCEI RHODESIENSE*: UTILISATION DIAGNOSTIQUE PAR LE PERSONNEL DE SANTÉ RURAL

Cette analyse fait partie d'une étude rétrospective (cas-témoins) sur la trypanosomiase portant sur 4 régions du nord-est de la Zambie, qui couvrent 5000 km^2 et dont la population est d'environ 10 000 habitants. On a interrogé et soumis à un examen clinique, selon un protocole normalisé, 60 sujets atteints de la maladie du sommeil, 60 témoins hospitalisés et 27 témoins du voisinage le plus proche, appariés pour l'âge et le sexe. L'adénopathie était significativement plus fréquente chez les malades que chez les témoins ($\chi^2 = 15,6$; $P < 0,001$, 1 degré de liberté), mais elle était plus souvent sous-maxillaire, axillaire, ou inguinale que cervicale postérieure. Les principaux signes d'une

atteinte du système nerveux central étaient les suivants: tremblement des doigts, perte de mémoire et altération des réflexes tendineux; toutefois, le réflexe cheiro-oral s'est révélé non spécifique car on le retrouvait fréquemment chez les témoins hospitalisés. Bien que la plupart des sujets se soient déclarés atteints depuis peu — les symptômes duraient en moyenne depuis 7 jours — près de 90% d'entre eux présentaient des anomalies du liquide céphalorachidien, caractérisées par une pléocytose et une augmentation de la protéinorachie. Chez les adultes dont la maladie était plus ancienne, on a remarqué une tendance significative du liquide céphalorachidien à contenir des trypanosomes. Huit symptômes étaient significativement plus fréquents chez les malades que dans les deux groupes témoins: céphalées, algies généralisées, hyperthermie, sommeil diurne excessif, œdème des jambes, malaise général, démangeaisons et douleurs articulaires. Certains d'entre eux ont été utilisés pour établir un système de cotation (sensibilité, 88,3%; spécificité, 81,7%) qui pourrait se révéler utile au personnel médical rural pour poser un diagnostic préliminaire de maladie du sommeil. Un système de cotation analogue, basé uniquement sur les signes physiques, était moins bon; l'association des symptômes et des signes physiques n'améliorait pas la sensibilité ni la spécificité de la méthode.

REFERENCES

1. UNDP/WORLD BANK/WHO CONSULTATION. Control of sleeping sickness due to *trypanosoma brucei gambiense*. *Bulletin of the World Health Organization*, **60**: 821–825 (1982).
2. WHO Technical Report Series No. 635, 1979 (*The African trypanosomiases*: report of a Joint WHO Expert Committee and FAO Expert Consultation).
3. WYATT, G. B. ET AL. Risk factors associated with the acquisition of sleeping sickness in north-east Zambia: a case-control study. *Annals of tropical medicine and parasitology*, **79**: 385–392 (1985).
4. BUYST, H. The epidemiology, clinical features and history of sleeping sickness on the northern edge of the Luangwa fly belt. *Zambian medical journal*, **8**: 2–12 (1974).
5. FOULKES, J. Human trypanosomiasis in Zambia. *Zambian medical journal*, **4**: 167–177 (1970).
6. DE RAADT, P. An observation on tendon reflexes during sleeping sickness, In: *East African Trypanosomiasis Research Organisation Annual Report 1965*. Tororo, East African Common Services Organisation, 1965, p. 53.
7. DE RAADT, P. & SEED, J. R. Trypanosomiasis causing disease in man in Africa. In: Julius, P. & Kreier, E. D., ed. *Protozoa of medical and veterinary interest*. New York, Academic Press, 1977.
8. WURAPA, F. K. ET AL. The public health importance of African trypanosomiasis in north-east Zambia. *Tropical and geographical medicine*, **36**: 329–333 (1984).
9. DAVEY, T. H. & WILSON, T. *The control of disease in the tropics*, 4th edition, London, H. K. Lewis, 1971.
10. FOULKES, J. R. Human trypanosomiasis in Africa. *British medical journal*, **283**: 1172–1174 (1981).