Contribution of tuberculosis to slim disease in Africa

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Abstract

***Objectives*—To assess the contribution of tuberculosis to the aetiology of the HIV wasting syndrome (slim) in Africa, a condition usually considered an enteropathy.**

***Methods*—Clinical examination and representative necropsy study of adult patients positive for HIV.**

***Setting*—Hospital medical wards in Abidjan, Ivory Coast.**

***Subjects*—Adults positive for HIV.**

***Main outcome measures*—CD4 T lymphocyte counts before death, clinical and anthropometric data, and gross and microscopic pathology.**

***Results*—Necropsy was done on 212 HIV positive adults. Tuberculosis was found in 41 of 93 with the clinical HIV wasting syndrome and in 32 of 119 without (odds ratio 2·1, 95% confidence interval 1·2 to 4·0). A significant association existed between the prevalence of tuberculosis at necropsy and the degree of cadaveric wasting (no wasting 25% (15/59); moderate wasting 40% (23/58); skeletal wasting 44% (42/95); P=0·02). Wasting was also associated with a history of chronic diarrhoea, but no association existed between diarrhoea and tuberculosis. Median CD4 T lymphocyte counts were lowest in wasted patients irrespective of findings at necropsy and in those with chronic diarrhoea ($<60\times10^6$/l).**

***Conclusion*—Wasting and chronic diarrhoea are late stage manifestations of HIV disease in Africa. The importance of tuberculosis as a contributing factor in the pathogenesis of the slim syndrome has been underestimated. In nearly half of patients dying with severe wasting, tuberculosis was the dominant pathological finding.**

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Introduction

The typical presentation of AIDS in adults in Africa is with severe wasting, diarrhoea, and fever; the term "slim" was introduced in Uganda in 1985 to describe this.[1] More than 80% of patients infected with HIV-1 admitted to hospital have lost over a tenth of their body weight, and over 40% have chronic diarrhoea.[2] These features were incorporated into the World Health Organisation's clinical case definition for AIDS surveillance in Africa[3] and later refined as the HIV wasting syndrome for resource poor countries.[4]

Four clinicopathological studies of diarrhoea and slim associated with HIV infection in Africa (Uganda, Zaire, and Zambia) have been published. The prevalence of coccidian infections (*Cryptosporidium* and *Isospora*) ranged from 20% to 61% and of microsporidiosis was 9%[5-9]; these infections were associated with increased permeability of the small intestine. It was concluded that slim has many causes including opportunistic enteropathogens, direct infection of mucosa by HIV, and malnutrition from malabsorption.

There have been no studies of the systemic pathology present in African patients with slim. Because tuberculosis is a common cause of death in African patients with HIV[10,11] we wondered whether tuberculosis could be a cause of the HIV wasting syndrome. We examined the relation in adults with HIV of wasting, diarrhoea, CD4 T lymphocyte counts, and pathological findings of tuberculosis at necropsy in west Africa.

Subjects and methods

For 10 months in 1991 consecutive adult patients (>14 years) admitted to the acute medical services of the largest hospital in Abidjan, Ivory Coast, were examined by a clinical team.[11] They were evaluated for the HIV wasting syndrome[4] and had blood taken for HIV serology[12] and for analysis of blood CD4 T lymphocytes.[13] No parasitological studies on faeces were performed.

A representative sample (24%) of HIV positive patients who died had necropsies with full histopathological evaluation. Body weight was not measured, but the cadavers were subjectively scored by the pathologists for wasting on a three point scale of no, moderate, and skeletal wasting.[11] To validate the assessment of wasting the heart was weighed. The average density of acid fast bacilli in tuberculosis lesions per cadaver was measured in histological sections on a logarithmic scale at magnification of ×400.[14] The quality of clinical diagnoses before death was too heterogeneous for comparison with necropsy pathology.

Analyses utilised Epi Info, version 5.01.[15] Statistical tests were calculations of odds ratio, χ^2 for trend, and linear regression; all tests were two tailed, and α was set at 0·05. The study was approved by the ethics and research subcommittee of the National AIDS Committee of the Ivory Coast.

Results

Two hundred and twelve HIV positive (162 men, 50 women) cadavers had necropsies. CD4 T lymphocyte counts before death were available for 96 (45%). Data on mortality and pathology are published elsewhere.[11] The emphasis here is on wasting, CD4 counts, diarrhoea, and tuberculosis.

WASTING, TUBERCULOSIS, AND CD4 T LYMPHOCYTE COUNTS

Of the 212 patients studied, 93 (44%) had been considered before death to have the HIV wasting syndrome. Patients with this syndrome had an increased prevalence of disseminated tuberculosis at necropsy (41/93 *v* 32/119; odds ratio 2·1, 95% confidence interval 1·2 to 4·0). Evaluation at necropsy showed 95/212 (45%) to be skeletally wasted. A linear decrease was found in heart weight, with increasing severity of wasting in men and women (table I)

supporting the validity of the gradation of wasting by the pathologist.

A significant linear trend existed between the degree of cadaveric wasting and the prevalence of tuberculosis at necropsy (table II). The severity of depletion of CD4 T lymphocytes correlated with the degree of wasting ($P<0.01$) and with the prevalence of tuberculosis at necropsy (table II). Density of acid fast bacilli in tuberculous lesions increased linearly with severity of wasting ($P<0.05$). The density increased with decreasing CD4 T lymphocyte count ($P<0.001$). Median densities were >100 per high power field in patients with skeletal wasting or with CD4 T lymphocyte counts $<50\times10^6$/l, or both.

TABLE I—*Distribution of weights of hearts measured at necropsy in patients positive for HIV**

	Degree of cadaveric wasting		
	None	Moderate	Skeletal
Men:			
No of observations	40	40	71
Mean (SD) heart weight (g)	316 (44)	265 (43)	236 (71)†
Women:			
No of observations	18	9	20
Mean (SD) heart weight (g)	233 (37)	218 (33)	200 (60)‡

*In 14/212 cadavers hearts not weighed.
†Linear regression $P<0.001$.
‡Linear regression $P<0.05$.

TABLE II—*Prevalence of tuberculosis at necropsy and median CD4 T lymphocytes counts among 212 patients positive for HIV according to degree of cadaveric wasting*

Measure	No wasting	Moderate wasting	Skeletal wasting
Prevalence of tuberculosis*	25% (15/59)	40% (23/58)	44% (42/95)
Median (interquartile range) CD4 cell count ($\times10^6$/l)	123 (57-311)	86 (23-157)	47 (22-104)

*χ^2 for linear trend=5·2, $P<0.02$.

WASTING, TUBERCULOSIS, AND CHRONIC DIARRHOEA

As shown in table II, cadavers with skeletal wasting assessed at necropsy were more likely to have tuberculosis than those with moderate or no wasting (42/95 *v* 38/117; 1·7, 0·9 to 3·0). Stratification by previously reported chronic diarrhoea did not influence the direction of this association.

Skeletally wasted patients were more likely to have reported chronic diarrhoea than those without skeletal wasting (47/95 *v* 41/115) 1·8, 1·0 to 3·2). Stratification for the presence of tuberculosis did not alter the association between wasting and chronic diarrhoea other than reducing the numbers and hence statistical power.

No association existed between tuberculosis and chronic diarrhoea. Intestinal lesions of tuberculosis were more common in skeletally wasted patients (15/95) than in patients without skeletal wasting (3/115; 7·0, 1·9 to 38·6), but their prevalence did not differ significantly in patients with and without diarrhoea when stratified for wasting (data not shown). In summary, these results suggest that tuberculosis and chronic diarrhoea were both significantly associated with skeletal wasting but were not associated with each other.

Table III shows the overall prevalence of tuberculosis and chronic diarrhoea in the 95 skeletally wasted patients. In addition to the 42 who had tuberculosis 25 had a history of chronic diarrhoea and 28 had neither tuberculosis nor chronic diarrhoea but had other AIDS defining pathology at necropsy.[11] Of the 42 skeletally wasted patients who had tuberculosis, just over half had given a history of chronic diarrhoea.

TABLE III—*Prevalence of tuberculosis and chronic diarrhoea in 95 HIV positive African patients with skeletal wasting*

Tuberculosis/chronic diarrhoea	No (%)
Tuberculosis alone	20 (21)
Chronic diarrhoea alone	25 (26)
Tuberculosis and diarrhoea	22 (23)
No tuberculosis or diarrhoea	28 (29)

WASTING, DIARRHOEA, TUBERCULOSIS, AND CD4 T LYMPHOCYTE COUNTS

Table IV shows the median CD4 T lymphocyte counts in patients with and without skeletal wasting according to whether they also had tuberculosis or chronic diarrhoea. Numbers are inadequate for statistical comparisons but crude trends are described. Severe depletion of CD4 T lymphocytes ($<60\times10^6$/l) was observed in all categories of patients with skeletal wasting. The patients with chronic diarrhoea had a low count irrespective of the presence or absence of wasting. Patients without skeletal wasting or chronic diarrhoea had higher counts ($>95\times10^6$/l), indicating that wasting and chronic diarrhoea are end stage manifestations of HIV infection.

TABLE IV—*Median (range) CD4 T lymphocyte counts ($\times10^6$/l) in patients positive for HIV at necropsy*

Condition	Skeletal wasting	Moderate/no wasting
Chronic diarrhoea	44 (19-75)	57 (29-130)
No chronic diarrhoea	50 (22-164)	136 (50-256)
Tuberculosis	47 (4-297)	113 (10-537)
No tuberculosis	47 (2-651)	99 (1-1013)

OTHER PATHOLOGIES

Of other potential causes of enteropathy, intestinal cryptosporidiosis was found in seven of 212 (3·3%) cadavers. Intestinal cytomegalovirus infection occurred in 15 of 212 (7%); in all but one it was focal and mild.

Discussion

This is the first study to analyse systemic pathology in relation to the clinical features and immune state of a large number of patients dying with slim disease in Africa. In such patients wasting and chronic diarrhoea were both associated with advanced immunodeficiency. Of patients with skeletal wasting, nearly half had suffered chronic diarrhoea before death and 44% had tuberculosis at necropsy; 29% had neither. Clear associations existed between the degree of immune deficiency, the severity of wasting, the prevalence of tuberculosis, and the density of acid fast bacilli in lesions. We found an association between the severity of wasting and history of chronic diarrhoea but not between chronic diarrhoea and tuberculosis nor between diarrhoea and tuberculosis of the intestine. Although no single cause can explain the pathogenesis of slim disease, these findings suggest that tuberculosis has been underestimated as a contributor to the development of this syndrome, which has been considered primarily an enteropathy.

The earlier studies of diarrhoea and slim associated with HIV infection in Africa were of heterogeneous patients at different stages of disease and immunodeficiency; pathological investigations were limited to intestinal material and results of absorption tests; extraintestinal tuberculosis was not sought or excluded, and a single patient with mycobacterial infection of the gut was noted.[5] (The original description of slim, however, did note that four of eight patients tested had acid fast bacilli in the sputum[1]).

Severe wasting results from reduced nutritional intake, malabsorption, increased catabolism, or a combination of these factors.[16] In the United States studies of HIV infection show that death from wasting is related to the magnitude of tissue depletion, independent of the underlying cause.[17] Secondary infections are potent causes both of increased resting energy expenditure and of anorexia with decreased energy intake.[16] Significant associations were noted between wasting and candidiasis, isosporiasis, and HIV encephalopathy, as were geographical differences in the prevalence of wasting.[18]

There is an impression that wasting is more severe among HIV positive patients in Africa than in indus-

Clinical implications

- Of all patients positive for HIV dying in a west African hospital nearly half were skeletally wasted (slim)
- At necropsy 44% of these wasted cadavers had multibacillary tuberculosis, and less wasted patients had less tuberculosis
- Diarrhoea was not associated with tuberculosis but was independently associated with wasting
- Earlier diagnosis and better management of tuberculosis is a priority in HIV infection in Africa

trialised countries[19]; because of the higher prevalences of coccidiosis found there it is presumed that the major cause of slim in Africa is infective enteropathy with secondary malabsorption.[2 5 8 19] There have been no complementary anthropometric or metabolic studies of HIV infection in Africa; furthermore, evaluations of the effects of dysphagia (due to oro-oesophageal lesions) and of poverty on nutrition are also lacking.[20]

In Africa the underlying causes of initial wasting associated with HIV infection are not known as natural history studies are lacking. Factors related to HIV infection may operate in the gut to cause malabsorption,[21] and food intake may fall for physical and social reasons. Slim undoubtedly has multiple pathogeneses. In our study chronic diarrhoea and tuberculosis were not present in all patients, other AIDS related illnesses can cause wasting, and wasting can occur as an isolated phenomenon in advanced HIV infection. Nevertheless, the high endemicity of tuberculous infection in Africa[22] results in an increasing proportion of HIV positive patients with disseminated disease as immunocompetence declines. Anthropometric studies show that tuberculosis is associated with malnutrition, and coinfection with HIV worsens the malnutrition.[23] Immunosuppression, dissemination of lesions, increasing bacillary load, and wasting interact and progress to death.

Our study suggests that the HIV wasting syndrome in Africa is not primarily an HIV associated enteropathy. In a substantial proportion of patients the dominant pathology is disseminated multibacillary tuberculosis. The implications are that prophylaxis or earlier diagnosis and treatment of tuberculosis in HIV positive people should be the aim; outcome in skeletally wasted patients is likely to be unfavourable whatever the cause.

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A MESSAGE I WOULD LIKE TO LEAVE BEHIND

The GP's diagnosis might be right

Two cases illustrate my message. A 4 year old boy fell over while walking around with a mouthful of peanuts. He promptly started coughing and wheezing. His mother brought him to the surgery the next day because she thought that he had inhaled a peanut. I agreed and had him admitted to hospital. No one thought that inhalation was the diagnosis and he was sent home with treatment for his asthma. There was little improvement and six weeks later I referred him again with the same diagnosis and a request for bronchoscopy. Again he was sent home with treatment for his "asthma." His mother and I were a little frustrated. Finally, two months after the initial episode he coughed up a peanut. His chest has been clear ever since.

A 42 year old woman was struck suddenly with symptoms which sounded like a subarachnoid haemorrhage. I requested her admittance with this diagnosis. I was aghast to see her two days later sitting in my waiting room. The diagnosis of migraine had been made but I felt that not enough had been done to exclude my original diagnosis. Her symptoms were worse, despite propranolol, and so I had her readmitted. A lumbar puncture was done, which showed a blood stained, xanthochromic fluid with a high protein concentration. "This may still not be a subarachnoid," I was told. At this point she was neurologically intact. Further investigations were unrevealing and she was sent home "with a clean bill of health," to quote her husband, who collected her. That night she had a frontal lobe bleed and was dead within three days. She was cremated without a necropsy. The husband came to ask why when I had got the diagnosis right on the first presentation she was now dead. I was at a loss for an explanation.

The lesson I would like to leave behind is this. Please prove the GP's original diagnosis wrong. This at least removes the doubt when the patient later turns up at the surgery "no better Doctor."—PAUL BOND *is a general practitioner in Richmond, North Yorkshire*