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Tuberculous meningitis in South African urban adults

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Summary

We retrospectively reviewed 56 adults with culture-proven tuberculous meningitis (TBM), investigating clinical signs, cerebrospinal fluid (CSF) findings and outcome. There were 50 patients, aged 18–59 years, 39 with and 11 without human immunodeficiency virus (HIV) infection. Six were aged 60 years or older. Neurological signs of TBM in 18–59-year-olds were unaffected by HIV serostatus while, compared to those $\geqslant$60 years of age, there were more patients with meningism (86.0% vs. 33.3%; $p=0.011$) and fewer with seizures (12.0% vs. 50.0%; $p=0.046$). The HIV-infected 18–59-year-olds had significantly more extrameningeal tuberculosis compared to the non-HIV-infected (76.9% vs. 9.1%; $p=0.0001$) and 23.1% had 'breakthrough' TBM. CSF analysis revealed 12 patients (21.4%) with acellular fluid (more common in those $\geqslant$60 years of age, $p=0.016$), of whom three had completely normal CSF. A neutrophil predominance was found in 22 patients (39.3%). Only three patients (5.4%) had a positive CSF smear for acid-fast bacilli. In-hospital mortality occurred in 39 patients (69.1%), was similar in all study groups, and was not related to neurological stage. The diagnosis of TBM can be masked by lack of meningism in the elderly and by atypical CSF findings.

Introduction

Tuberculous meningitis (TBM), which continues to cause high morbidity and mortality rates, has acquired added significance in the era of human immunodeficiency virus (HIV) infection, with studies in Spain[1] and the Ivory Coast[2] showing a markedly increased risk for TBM in HIV-infected patients with tuberculosis. Most reports on TBM in adults in the 1990s have focused on developed countries.[1,3–8] These patient populations may not reflect TBM as seen in developing countries.

In South Africa, tuberculosis is endemic, with estimated case rates exceeding 400/100 000 population,[9] while there were an estimated 1.8 million adults infected with HIV by 1996.[10] In Soweto, South Africa, TBM is the commonest cause of adult meningitis.[11]

This study was performed in order to describe the clinical presentation, cerebrospinal fluid findings, and outcome of TBM in adults at Chris Hani Baragwanath Hospital, Soweto, South Africa.

Methods

Chris Hani Baragwanath Hospital is a 3300-bed public university hospital serving an estimated population of 3 million people. The patient population included adults who had *Mycobacterium tuberculosis* cultured in cerebrospinal fluid (CSF) between March 1994 and March 1997. Patients were excluded if they had abnormal CSF findings due to a bloody tap, if they were $<$60 years of age and were not tested for HIV antibodies, or if there was an alternative cause for their neurological presentation with the only evidence for tuberculosis being a culture from a single specimen of CSF.

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The remaining patients were divided into three groups: HIV-seropositives aged 18–59 years, HIV-seronegatives aged 18–59 years, and patients older than 59 years. Their case records were reviewed using a protocol to identify demographic characteristics, laboratory and radiological data, and outcome. Their neurological status at the time of CSF examination was classified into three stages according to criteria established by the Medical Research Council.[12] Patients in stage 1 were fully conscious and rational with or without meningeal signs, but with no focal neurological signs. Stage 2 patients were confused or had focal neurological signs such as cranial nerve palsies or hemiparesis. In stage 3, patients had either deep coma or delirium or dense hemiplegia or paraplegia. Deaths occurring on the initial admission only were noted.

Cerebrospinal fluid was examined routinely for cell count and biochemistry. CSF was concentrated and examined by fluorescent microscopy using an auramine stain for acid-fast bacilli. Concentrated specimens were inoculated on to both a Lowenstein-Jensen medium and into a Bactec 12B vial (Middlebrook 7H12 agar) for culture. Susceptibility testing was performed using the Bactec system.

The χ^2 or Fisher's exact tests were used in the analysis. Values of $p < 0.05$ were considered statistically significant.

Results

Eighty-five patients were originally identified, of whom 10 had missing bedletters, seven were aged 18–59 years and had unknown HIV serostatus, seven had another cause for their neurological presentation and five had a bloody tap. Fifty-six patients met the selection criteria and were analysed, including 39 HIV-infected and 11 non-HIV-infected individuals aged 18–59 years and six patients aged 60 years and older. None of this last group had clinical findings suggestive of HIV infection; the only person tested was HIV-seronegative.

All the subjects had abnormal neurological symptoms or signs before tuberculous meningitis was diagnosed. Initial symptoms and duration of illness were available in too few patients for analysis to be performed. Clinical signs at presentation were similar in 18–59-year-olds irrespective of HIV serostatus except for a significant increase in HIV-seropositives with clinical or radiological findings suggestive of extrameningeal, predominantly pulmonary, tuberculosis ($p = 0.0001$) (Table 1).

In those $\geqslant 60$ years of age compared to 18–59-year-olds, there was significantly less meningism ($p = 0.011$) and more frequent seizures ($p = 0.046$). Nine (23.1%) of the HIV-infected had been on antituberculous therapy for durations ranging from 3 days to 5 months before symptoms or signs of tuberculous meningitis became apparent and lumbar puncture was performed. This situation has been called 'breakthrough' TBM. Three of these nine were referred from TB sanatoria, while no data were available on the compliance to treatment of the other six. The CD4 lymphocyte count on admission was available for 21 HIV-infected patients (53.8%) who had a mean result of 172/mm^3 and a median of 128/mm^3 (range 36–464/mm^3). Underlying medical conditions other than HIV infection were found in 11 patients including alcoholism (7), diabetes mellitus (2) and corticosteroid treatment (2). One HIV-infected patient had a concomitant pneumococcal meningitis.

Analysis of CSF revealed 12 patients (21.4%) with acellular fluid, which was significantly more common in those $\geqslant 60$ years of age, compared to 18–59-year-olds ($p = 0.016$) (Table 2). The three patients who had an entirely normal CSF analysis all had evidence of extrameningeal tuberculosis—two had pulmonary tuberculosis and one had miliary tuberculosis. A normal protein level was found in eight patients (14.3%) and a normal glucose level in 12 (21.4%). Only 15 patients (26.8%) had typical CSF findings of tuberculous meningitis (lymphocyte predominance with raised protein and a low glucose level), while 22 (39.3%) had a neutrophil predominance. A positive smear for acid-fast bacilli was found in three patients (5,4%). Of the 47 patients for whom drug susceptibilities were available, five (10.6%) had organisms resistant to either isoniazid or rifampicin and two (4.3%) had tuberculosis resistant to both drugs (multidrug resistance). Two of these patients had 'breakthrough' TBM. CT brain scans were performed on 15 patients; only two were initially normal. Abnormalities found included five scans with cerebral infarction, three with hydrocephalus, and one each with basal meningeal enhancement, cerebritis, tuberculoma, cerebral atrophy and white matter degeneration.

Death, while hospitalized for diagnosis and initial treatment of tuberculous meningitis, occurred in 39 patients (69.6%) (Table 3). There was no significant difference in outcome by neurological stage or age group. Ten patients (17.9%) received no therapy, of whom seven died and three were discharged prior to the diagnosis being considered. There was a significant difference in mortality between those who started antituberculosis treatment within 24 h of admission (14/25 died, 56.0%) and those in whom therapy was delayed for at least 24 h, (19/21 died, 90.5%) ($p = 0.024$). Seven of those with delayed treatment had lumbar punctures postponed until after CT brain scans were performed, for which they had to wait at least 24 h. Only six patients received

Table 1 Patient characteristics in tuberculous meningitis according to age, and HIV serostatus in those aged 18–59 years

	18–59 years		⩾60 years (*n*=6)
	HIV-infected (*n*=39)	Non-HIV (*n*=11)	
Mean age (years)	33.9	33.1	68.5
Age range (years)	20–54	18–50	61–80
Male:female ratio	1.44	0.83	1.24
Signs			
Temperature ⩾38 °C	28(71.7%)	5(45.4%)	2(33.3%)
Meningeal signs*	34(87.2%)	9(81.8%)	2(33.3%)
Altered mentation	29(74.4%)	8(72.7%)	5(83.3%)
Focal deficits**	10(25.6%)	4(36.4%)	3(50.0%)
Seizures***	5(12.8%)	1(9.1%)	3(50.0%)
Extrameningeal tuberculosis****	30(76.9%)	1(9.1%)	3(50.0%)

* $p=0.011$ ⩾60 years vs. 18–59 years. ** Excluding sixth-nerve palsy. *** $p=0.046$ ⩾60 years vs. 18–59 years. **** $p=0.0001$ HIV-infected vs. non-HIV. p=NS all other comparisons.

Table 2 Cerebrospinal fluid findings in tuberculous meningitis according to age, and HIV serostatus in those aged 18–59 years

	18–59 years		⩾60 years (*n*=6)
	HIV-infected (*n*=39)	Non-HIV (*n*=11)	
White cell count ($\times 10^6$/l)			
Mean	152	69	17
Median	57	11	0
Range	0–777	0–404	0–60
Lymphocytes >50% (*n*)	14(35.9%)	7(63.6%)	1(16.7%)
Acellular (*n*)*	6(15.4%)	2(18.2%)	4(66.7%)
Protein (g/l)			
Mean	3.37	1.55	1.61
Median	2.13	1.59	0.8
Range	0.25–23.1	0.37–2.28	0.42–5.4
Normal (<0.5 g/l) (*n*)	4(10.3%)	2(18.2%)	2(33.3%)
Glucose (mmol/l)			
Mean	2.1	2.4	3.5
Median	1.6	1.9	3.6
Normal (⩾2.2 mmol/l), or ⩾50% of blood glucose level) (*n*)	10(25.6%)	0	2(33.3%)
Normal CSF (*n*)	2(5.1%)	0	1(16.7%)

* <5 lymphocytes and no neutrophils; $p=0.016$ ⩾60 years vs. 18–59 years. All other comparisons, p=NS.

corticosteroids, all of whom died. All three patients with normal CSF died, as did seven of the nine on antituberculous therapy prior to admission and six of the seven with resistant organisms. Death occurred in 7/9 (77.8%) patients with CD4 <100/mm^3, 3/5 (60%) with CD4 100–200/mm^3 and 6/7 (85.7%) with CD4 >200/mm^3 (p=NS).

Comparison of clinical presentation and outcome between those with acellular fluid and those with a white blood cell pleocytosis in CSF revealed no significant differences other than significantly less frequent meningism in those with acellular fluid ($p=0.045$) (data not shown).

Discussion

The clinical and laboratory manifestations and outcome of TBM among AIDS patients did not differ significantly from those of non-HIV-infected subjects, confirming the findings of other series.[1,7,8] Diagnosis of TBM was facilitated by the frequent occurrence

Table 3 Outcome of tuberculous meningitis by stage of disease according to age, and HIV serostatus in those aged 18–59 years

Stage	18–59 years				⩾60 years	
	HIV-infected ($n=39$)		Non-HIV ($n=11$)		($n=6$)	
	n	Died	*n*	Died	*n*	Died
1*	7(17.9%)	4(57.1%)	2(18.2%)	0	1(16.7%)	0
2	25(64.1%)	19(76.0%)	5(45.5%)	3(60.0%)	2(33.3%)	1(50.0%)
3	7(17.9%)	5(71.4%)	4(36.4%)	4(100.0%)	3(50.0%)	3(100.0%)
Total deaths (*n*)		28(71.8%)		7(63.6%)		4(66.7%)

*Of the two patients without meningism, one had had a seizure, the other a psychotic episode, prior to admission. $p=$NS for all comparisons.

of tuberculosis outside the central nervous system, which was significantly more common among the HIV-infected. Extrameningeal tuberculosis has been found in 41–68% of patients in other studies,[1,4–7] which is lower than the 76.9% of HIV-infected in our study, but similar to the 60.7% overall. 'Breakthrough' TBM, which has been described[1,6,7,14] would seem to be predominantly, though not exclusively, related to poor compliance[7] or drug-resistant tuberculosis.

The two major problems identified in this study were the presence of obstacles to a timely diagnosis of TBM and the extremely high mortality. The difficulty in establishing the diagnosis of TBM is well recognized.[13] The absence of meningism, which is more common in the elderly,[14] requires a high index of clinical suspicion. In resource-poor countries, patients with focal signs or elderly patients with seizures may have significant delays before lumbar puncture while awaiting a CT brain scan. Atypical CSF findings may add to the difficulties of diagnosis in the form of neutrophil predominance, acellular or even normal CSF, especially if there is a low yield of direct smear for acid-fast bacilli. Acellular CSF in TBM has been noted in both HIV-seropositive and non-HIV infected patients,[1,4,7,8,11,14,15] while a completely normal CSF has been found in HIV-seropositives.[1,7] In a subanalysis of a Spanish study, 4/25 AIDS patients at one hospital had acellular CSF, none of whom experienced headaches and only one of whom had meningeal signs.[16] Although all patients in this study had neurological symptoms or signs, meningism was significantly less common in the patients with acellular CSF, a combination which may delay diagnosis in the absence of extrameningeal tuberculosis. Fortunately, all but three of the patients with acellular CSF had abnormal chemistry and the three subjects with normal CSF all had evidence of tuberculosis outside the central nervous system. None of the patients with acellular CSF had second lumbar punctures to assess whether pleocytosis had developed. Early-stage patients and those who present acutely may have a neutrophil predominance and near-normal chemistry in the initial lumbar puncture; such neutrophil predominance has been seen in 22–32% of patients in other studies.[1,3,4,6,11,14,15] A low yield on direct smear of CSF, i.e. less than 15%, is not uncommon[3,4,6,14] although it can be increased to 87% with large volumes of CSF and repeated lumbar punctures.[15]

Mortality rates of TBM in published studies range from 3–70% with most recent series reporting mortality below 35%.[1,3,5,8,14,15] The high death rates occurred in series where medical care was instituted late in the course of the disease[18] or where patients were mostly in neurological stage 3.[6] In our study, the duration of illness was not available, and mortality was not significantly related to stage of illness, possible due to the small numbers of patients. Corticosteroids were used in only six patients, none of whom survived. The fact of culture positivity in CSF may itself have been a major poor prognostic factor.[19] Delays in therapy of >24 h resulted in a higher mortality, leaving little margin for error in diagnosis.

The results of this study may not be applicable to all adults with TBM in our setting due both to the small numbers of both patients aged 60 years and older, and non-HIV-infected 18–59-year-olds, as well as the strict inclusion criteria used. Mortality was 40% in a previous study of TBM at this hospital in which a broader definition of TBM was used, with only 21% of patients having CSF cultures which were positive.[11]

A great need exists for a rapid, sensitive, cheap and easily applied test for TBM. Until such a test becomes available, a high index of suspicion for TBM, coupled to the testing of large volumes of CSF repeatedly in suspicious cases, remains the only route to a more rapid diagnosis.

References

1. Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A, Gonzalez-Lahoz J, Bouza E. Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med* 1992; **326**:668–72.
2. Lucas SB, Hounnou A, Peacock C, Beaunel A, Djomand G, N'Gbichi JM. The mortality and pathology of HIV infection in a West African city. *AIDS* 1993; **7**:1569–79.
3. Jensen TH, Magnussen P, Eriksen NHR, Skinhoj P. Tuberculous meningitis: 23 cases from a 12-year period (1976–1987). *Dan Med Bull* 1990; **37**:459–62.
4. Davis LE, Rastogi KR, Lambert LC, Skipper BJ. Tuberculous meningitis in the southwest United States: a community-based study. Neurology 1993; **43**:1775–8.
5. Kent SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculous meningitis: A 30-year review. *Clin Infect Dis* 1993; **17**:987–94.
6. Verdon R, Chevret S, Laissy J-P, Wolff M. Tuberculous meningitis in adults: Review of 48 cases. *Clin Infect Dis* 1996; **22**:982–8.
7. Yechoor VK, Shandera WX, Rodriguez P, Cate TR. Tuberculous meningitis among adults with and without HIV infection. Experience in an urban public hospital. *Arch Intern Med* 1996; **156**:1710–16.
8. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. *Am J Med* 1992; **93**:520–4.
9. Medical Research Council. *National Tuberculosis Research Programme. Annual Report*. Cape Town, 1997–1998.
10. Department of National Health. Seventh national HIV survey of women attending antenatal clinics of the public health services, October/November 1996. *Epidemiological Comments* December 1996/January 1997; **23**:4–11.
11. Bergemann A, Karstaedt AS. The spectrum of meningitis in a population with high prevalence of HIV disease. *Q J Med* 1996; **89**:499–504.
12. Medical Research Council Report. Streptomycin treatment of tuberculous meningitis. *Lancet* 1948; **i**:582–96.
13. Ogawa SK, Smith MA, Brennessell DJ, Lowy FD. Tuberculous meningitis in an urban medical centre. *Medicine (Baltimore) 1987;* **66**:317–26.
14. Nagami PH, Yoshikawa TT. Tuberculosis in the geriatric patient. *J Am Geriatr Soc* 1983; **31**:356–63.
15. Kennedy DH, Fallon RJ. Tuberculous meningitis. JAMA 1979; **241**:264–8.
16. Laguna F, Adrados M, Ortega A, Gonzalez-Lahoz JM. Tuberculous meningitis with acellular cerebrospinal fluid in AIDS patients. *AIDS* 1992; **6**:1165–7.
17. Norris AH, Buckley M. Central nervous system tuberculosis. In Rossman MD, MacGregor RR, eds. *Tuberculosis: clinical management and new challenges*. New York, McGraw-Hill, 1995:157–71.
18. Kilpatrick ME, Girgis NI, Yassin MW, Abu el Ella AA. Tuberculous meningitis—clinical and laboratory review of 100 patients. *J Hyg (Lond)* 1986; **96**:231–8.
19. Traub M, Colchester ACF, Kingsley DPE, Swash M. Tuberculosis of the central nervous system. *Q J Med* 1984; **209**:81–100.