Tuberculous meningoencephalitis in Baghdad, 1993–99: a clinical study of 224 cases

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التهاب السحايا والدماغ السلي في بغداد، 1993–1999، دراسة سريرية على 224 حالة

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الخلاصة: درست هذه الورقة جميع حالات التهاب السحايا والدماغ السلي التي أدخلت في مستشفى ابن الخطيب للأمراض السارية في بغداد في الفترة 1993-1999. وقد ارتكز التشخيص على قصة المريض والموجودات السريرية وتحليل السائل النخاعي واستفراد الجراثيم والاستجابة للمعالجة الدوائية للسل. وقد قورنت الموجودات في الحالات التي شُخِّصت إصابتها بالتهاب السحايا والدماغ السلي بالموجودات بالتهابات السحايا من الأنماط الأخرى. وكان هناك 224 حالة تشكّل 5٪ من مجمل عدد حالات التهاب السحايا التي أُدخلت إلى المستشفى خلال هذه الفترة. وكانت نسبة إصابة الذكور إلى الإناث 1.4 إلى 1. وكان معدّل العمر يتراوح بين ستة أشهر إلى 72 عاماً، وكان المعدل العام لوفيات الحالات 21٪.

ABSTRACT This study examined all cases of tuberculous meningoencephalitis admitted to Ibn El-Khateeb Hospital for Infectious Diseases in Baghdad from 1993 to 1999. The diagnosis was based on the patient's history, clinical findings, cerebrospinal fluid analysis, microbial isolation and response to antitubercular drug therapy. The findings for cases diagnosed with tuberculous meningoencephalitis were compared with other types of meningitis. There were 224 cases comprising 5% of the total number of meningitis cases admitted during this period. The male to female ratio was 1.4:1. The age range was from 6 months to 72 years and the overall case fatality rate was 21%.

La méningo-encéphalite tuberculeuse à Bagdad, 1993-1999 : étude clinique de 224 cas

RESUME Cette étude a examiné tous les cas de méningo-encéphalite tuberculeuse admis à l'Hôpital des maladies infectieuses Ibn El-Khateeb à Bagdad de 1993 à 1999. Le diagnostic était fondé sur les antécédents du patient, les résultats de l'examen clinique, l'analyse du liquide céphalo-rachidien, l'isolement du microbe et la réponse au traitement antituberculeux. Les résultats pour les cas de méningo-encéphalite tuberculeuse diagnostiquée ont été comparés avec d'autres types de méningite. Il y avait 224 cas qui constituaient 5 % du nombre total de cas de méningite hospitalisés pendant cette période. Le rapport hommes-femmes était de 1,4 pour 1. L'âge des patients était compris entre 6 mois et 72 ans et le taux de létalité global était de 21 %.

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Introduction

Tuberculosis (TB) is still a major public health challenge to the world especially in developing countries [*1–7*]. According to information produced by the coordinating team of the World Health Organization's Stop TB initiative there are 16–20 million cases of TB prevalent globally with 8 million new cases annually [*7*]. TB accounts for 2 million deaths annually and is the largest cause of death among people with human immunodeficiency virus (HIV) infection and among women of reproductive age.

The involvement of the central nervous system is always secondary to a primary lesion elsewhere [*1,8–12*]. Of all forms, TB of the nervous system is the most serious, constituting 4%–6% of the extrapulmonary cases [*1,13–15*]. Meningitis is the most common manifestation of neurotuberculosis [*1,10–12,16*]. No part of the central nervous system (CNS) is spared; the disease can affect all tissue components of the brain and its coverings [*1,15*]. Infection of the meninges by TB bacilli is usually caused by rupture of the subependymal tubercle into the subarachnoid space rather than by haematogenous seeding of the meninges. It can also be a complication of miliary TB [*6–8,10*]. TB of the CNS can manifest itself as meningitis, encephalitis or encephalopathy, tuberculoma, vasculitis or arteritis, spinal arachnoiditis, radiculomyelitis and even behavioural changes or demyelination to a lesser extent [*1,8,9,15*].

The diagnosis of tuberculous meningoencephalitis (TBM) can be difficult in the absence of microbial isolation, as the clinical presentation is often deceptive and the response to treatment is not as satisfactory as in pyogenic meningitis [*1,17,18*]. The key to diagnosis of infections is the isolation of the causative microorganism from the tissues involved; in the case of TBM, TB bacilli can be isolated directly by Ziehl-Neelsen stain or cultured from the cerebrospinal fluid (CSF). However, these tests are not routinely available in developing countries [*1,16–18*]. Other sophisticated tests of high sensitivity but with lower specificity are also unavailable, including adenosine deaminase, protease inhibitors and tuberculostearic acid [*1,15,17*]. The latex agglutination test is promising [*19*], and DNA probing is a recent technique for detection of tuberculous antigen or antibody in the CSF [*1*]. C-reactive protein, lactate dehydrogenase, lactic acid and bromide fractionation tests have also been described [*1,20*].

Suspected cases of CNS infection are usually referred from hospitals and clinics to the Ibn El-Khateeb Hospital for Infectious Diseases in Baghdad for further evaluation, diagnosis and treatment. This paper documents 224 cases of TBM admitted to the hospital over a 7-year period and compares the clinical picture with that of meningitis of pyogenic origin.

Methods

All cases of CNS infection in the hospital from 1993 to 1999 were investigated to determine the final diagnosis. In the absence of microbial isolation, the diagnosis was based on the best epidemiological, clinical and laboratory findings. The outcome of the TBM cases was recorded.

Blood samples were taken from every patient with signs of CNS infection to determine white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), haemoglobin (HB) level and serum cultures. All patients had a chest X-ray. Other test and examinations were used when indicated: serum osmolarity, urinary sod-

ium and antidiuretic hormone (ADH) levels, computerized tomography (CT) scan and magnetic resonance imaging (MRI). Liver and renal function tests were not routinely used.

CSF samples were taken from suspected cases of TBM at least three times with a further one to three times for clinical follow-up every three months. The CSF was analysed for colour, cobweb test, cell counts and type of cells, glucose and protein levels, Gram stain and Ziehl–Neelsen stain and CSF culture. The latex agglutination test for the common pyogenic causes of meningitis was also carried out. The patient's BCG vaccination status was noted.

The drugs used for treatment of TBM cases were isoniazid, streptomycin , rifampicin, pyrazinamide and ethambutol for at least 15–18 months, according to World Health Organization's recommendations at the time, prior to the Directly Observed Treatment, short-course (DOTS) strategy.

Results

The total number of cases of CNS infection (meningitis, meningoencephalitis) admitted to the hospital during the seven years (1993–99) was 4482; of these 71% were pyogenic meningitis, 24% viral meningitis and 5% TBM. Of the 224 cases of TBM, 131 were males and 93 females, giving a male:female ratio of 1.4:1 (Table 1). Table 1 also shows the age distribution of cases, which ranged from 6 months to 72 years. The monthly distribution of cases (Figure 1) shows admission of TBM cases throughout the year with peaks in March and around July/August.

The main clinical features of TBM were fever (92%), lassitude (90%), weight loss (88%), vomiting (74%), anorexia (72%),

Table 1 **Distribution of cases of tuberculous meningoencephalitis and case fatality rate according to age and sex**

Age group (years)	Males No.	Females No.	Total No.	Total %	Case fatality rate (%)
<5	42	25	67	30	19
6–10	11	7	18	8	17
11–15	6	5	11	5	9
16–20	8	12	20	9	10
21–25	7	10	17	8	18
26–30	12	8	20	9	20
31–35	5	4	9	4	22
36–40	6	9	15	7	27
41–45	8	5	13	6	23
46–50	6	3	9	4	33
51+	20	5	25	11	26
Total	131	93	224	100	21

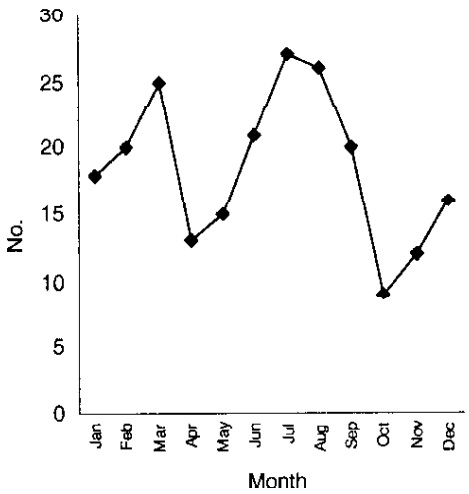

Figure 1 **Monthly distribution of cases of tuberculous meningoencephalitis**

headache (60%), altered consciousness (48%), sleep disturbances (38%) and cough (24%). The main signs were raised temperature (92%; mean 38.2 °C), neck stiffness (88%), Brudzinski's sign (69%), Kernig's sign (67%), papilloedema (36%), neurological deficit (16%) and cranial nerve palsies (95%).

The overall case fatality rate was 21% (Table 1). Full clinical improvement was seen in 63% of cases and complications developed in 36 cases (16%). The complications were mainly lack of memory and concentration (34%), emotional lability (32%), deafness (32%), blindness (28%), oculomotor problems (28%) and other nerve palsies (54%).

In all, 80 cases (36%) had received BCG vaccination and the case fatality rate for these patients was 13%. This compared with a case fatality rate of 26% for the 144 cases without BCG vaccination.

Table 2 compares the blood tests for patients with TBM and pyogenic meningitis. The most important finding was the peripheral WBC count, the mean of which was 10.3×10^3 per mm^3 for pyogenic and 5.4×10^3 per mm^3 for TBM cases respectively. The serum osmolarity of TBM cases was lower than for pyogenic meningitis.

Table 3 shows the detailed CSF findings for six sequential samples from TBM cases. The CSF findings for cases with pyogenic meningitis are compared with TBM cases on Table 4.

Discussion

TBM is always secondary to a primary lesion elsewhere and so its incidence tends to be parallel to that of the primary disease [*1,6–10*]. If not recognized early and treated promptly, TBM is nearly always fatal [*1,6–12*]. However, the response to treatment for TBM is not as rapid as that for pyogenic meningitis, added to which there is a higher rate of complications with TBM and increased multiresistance of the TB bacilli to antitubercular drugs [*1,15–17*].

As reported elsewhere, this study showed that TBM comprised 5% of the total admissions of meningitis cases to the hospital and mainly affected the younger age groups [*6–12,16*]. As in other studies, TBM occurred in every month of the year.

The complaints of fever, vomiting and sensory disturbances, and signs of meningeal irritation and the higher rank of cranial nerve palsies, were the commonest clinical

Table 2 **Comparison of mean haematocrit values between pyogenic meningitis and tuberculous meningoencephalitis**

Type of meningitis	WBC count (/mm^3)	ESR (mm/h)	Hb level (g/dL)	Serum osmolarity (mosmol/L)
Pyogenic (n = 543)	10.3×10^3	60	12.8	275 (n = 164)
Tuberculous meningoencephalitis (n = 224)	5.4×10^3	38	11.2	248 (n = 58)

WBC = white blood cell.
ESR = erythrocyte sedimentation rate.
Hb = haemoglobin.

Table 3 **Results of cerebrospinal fluid (CSF) analysis for cases of tuberculous meningoencephalitis (*n* = 224)**

Value	Sample of CSF					
	1st	2nd	3rd	4th	5th	6th
Colour (% of cases)						
Clear	26	80	92	100	100	100
Xanthochromic	40	15	7	0	0	0
Opalescent	33	5	1	0	0	0
Turbid	1	0	0	0	0	0
Cobweb	58	5	0	0	0	0
Mean cell count (/mm³)	156	86	52	24	9	5
Mean lymphocyte level (%)	82	89	96	100	100	100
ZN stain (% of cases positive)	5	0	0	0	0	0
CSF culture (% of cases positive)	8	0	0	0	0	0
Mean protein level (mg/dL)	184	178	142	86	76	52
Mean glucose level (mg/dL)	36	41	44	58	66	68
Mean serum sodium level (mEq/L)	128.7	134.2	142.0	0	0	0

Table 4 **Comparison of cerebrospinal fluid (CSF) analysis for cases of pyogenic meningitis and tuberculous meningoencephalitis**

Type of meningitis	Colour	Mean cell count (/mm³)	Mean protein (mg/dL)	Mean glucose (mg/dL)	Stain (% cases positive)	Culture (% cases positive)
Pyogenic (*n* = 543)	Turbid	1620 (> 95% polymorpho-nuclear cells)	256	28	64 (Gram)	40
Tuberculous meningo-encephalitis (*n* = 224)	Clear, xanthochro-mic, opalescent	156 (82% lymphocytes)	184	36	5 (ZN)	8

findings of TBM, as reported elsewhere [*1,8,10,16*].

Differentiating TBM from other types of meningitis and CSF infections is not always easy; in the absence of microbial isolation from the CSF the so-called 'predictive value' of CSF analysis is still confusing, especially in partially-treated pyogenic meningitis [*17,22–25*]. However, the peripheral WBC count was found to be a valid laboratory test in this study because pyogenic meningitis cases are usually characterized by rapid onset with peripheral neutrophilic leukocytosis while the TBM

cases here showed a longer prodromal history and their peripheral WBC counts were normal.

Another valid sign demonstrated in this study was the formation of a mesh work of the CSF 'cobweb' after 24 hours standing at room temperature [*1,6*]. It was noted that the cell count and the protein and glucose values in CSF did not return to normal until at least 3 months of treatment with antitubercular drugs. This contrasts with the observation that CSF findings for pyogenic and viral meningitis usually returned to normal after 2 weeks of treatment with antibiotics [*16,21,22*].

The decreased serum osmolarity among the patients with TBM might be evidence of the syndrome of inappropriate release of antidiuretic hormone (SIADH), as the increased urinary excretion of sodium ions was present despite the presence of a significant state of hyponatraemia.

The BCG vaccination status was also found to be important in this study. It appeared that BCG vaccination offered significant protection against both the morbidity and mortality of TBM. Similar findings on the outcome of tuberculosis in general and on TBM have been reported from India, Turkey and elsewhere [*1,14, 26–28*].

We previously reported 161 cases of TBM during the 7 years preceding this study (1986–92) [*16*]. The increase in TBM cases from 1993–99 reported here might be directly related to the effects of war and poverty, and subsequent undernutrition, on the Iraqi people after the international sanctions against Iraq after the Gulf war of 1991. Similar findings of the effect of conflict have been reported from El Salvador [*13*].

It can be concluded that TBM is still a common and serious type of extrapulmonary tuberculosis in developing countries, associated with a high mortality rate and significant complications. Resources for the final diagnosis of TBM are still limited or unavailable in most hospitals in the developing world. Added to this, the CSF findings alone might be confusing to the diagnosis, and normal chest X-ray and negative tuberculin testing might be found among 50% or more of TBM cases [*1,16, 17*]. Early and rapid treatment with antitubercular drugs is needed when there is a high clinical suspicion of TBM [*16,18*].

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Strategic plan for tuberculosis control in the Eastern Mediterranean Region 2002-2005

The Vision of the strategic plan is to eliminate TB in the Region by 2050 so that "the first children born in this millennium in the Region will see TB eliminated in their lifetime". The Mission is to significantly reduce the burden of TB in the Region by ensuring that:

- Every TB patient has access to effective diagnosis, treatment and cure;
- Transmission of TB is stopped;
- Inequitable social and economic toll of TB is reduced; and
- All relevant partners in health, social and economic development are involved in TB control activities.

The regional targets set are:

By 2005, detect at least 70% of all cases of TB, and successfully treat at least 85% of them, and sustain the achievements.

By 2005, enrol all detected TB patients in the DOTS strategy.

By 2010, reduce prevalence and deaths by 50%.

More information on the TB control programme in the WHO Eastern Mediterranean Region can be found at: http://www.emro.who.int/STB/strategicplan.htm