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Tuberculous meningitis – clinical and laboratory review of 100 patients

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SUMMARY

In developing countries tuberculous meningitis is a difficult infection to differentiate from other central nervous system (CNS) infections. This paper presents the history, physical findings, laboratory data, and clinical course of 100 patients who were admitted to a special ward and had CSF cultures positive for *Mycobacterium tuberculosis*. Fifty-four patients were comatose when admitted and 76 had meningeal signs. Mean admission CSF values were WBC 531, glucose 23 mg/dl, and protein 166 mg/dl. Only two CSF AFB smears were positive. Sixty-one percent of the chest X-rays taken were consistent with pulmonary tuberculous and 39% were normal. Twenty-four patients died within the first week after admission, before the clinical diagnosis was made and anti-tuberculous therapy could be started. Fifty-three of 76 patients given antituberculous therapy died. Neurologic sequelae developed in 48% of the survivors. The high mortality and morbidity rates in this patient-group were due to the severity of illness on admission and the predominance of children (54%).

INTRODUCTION

Current clinical and laboratory methods for the prompt diagnosis of tuberculous meningitis are at best inadequate. The only definitive diagnostic laboratory test for *Mycobacterium tuberculosis* is bacteriological culture of the CSF of patients, and this requires up to 6–8 weeks (Good, Silcox & Kilburg, 1981). Partially treated purulent meningitis often presents CSF findings similar to tuberculous meningitis (Quaade & Kristensen, 1962). Data of several investigators revealed that only 48% of the CSF samples examined from a total of 1098 patients suspected of having tuberculous meningitis were culture positive (Voljavec, Orton & Corpe, 1959; Lincoln, Sordillo & Davies, 1960; Weiss & Flippin, 1965; Osuntokun, Adeuja & Familusi, 1971; Bobrowitz, 1972; D'Oliveria, 1972; Steiner & Portugaleza, 1973; Escobar *et al.* 1975; Sumaya *et al.* 1975; Visudhiphan & Chiemchanya, 1975; Cardozo, Raidoro & Patel, 1976; Girgis *et al.* 1976; Idriss, Sinno & Kronfol, 1976; Haas *et al.* 1977; Bwibo, 1979; Kennedy & Fallon, 1979).

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Mortality from tuberculous meningitis depends on patient age, clinical condition at admission, length of delay in starting therapy, and therapy used (Lincoln & Sifontes, 1953; Lorber, 1954; Forbes, 1960; Weiss & Flippin, 1965; Idriss, Sinno & Kronfol, 1976; Kennedy & Fallon, 1979). Intrathecal therapy combined with systemic therapy has been reviewed elsewhere (Lorber, 1954; Smith, 1956; Forbes, 1960; Fitzsimons & Smith, 1963; Hockaday & Smith, 1966; Freiman & Geefhuysen, 1970; Ware, 1971). The introduction of several antituberculous drugs which achieve therapeutic CSF levels when administered systemically (Place, Pyle & Huerga, 1969; Freiman & Geefhuysen, 1970; Bobrowitz, 1972; D'Oliveria, 1972; Girgis *et al.* 1976; Bobrowitz, 1979; Ostrow, 1979) had made systemic therapy standard (Debre & Brissaud, 1956; Lincoln, Sordillo & Davies, 1960; Steiner & Portugaleza, 1973; Sifontes, 1975; Sumaya *et al.* 1975; Visudhiphan & Chiemchanya, 1975). The addition of steroids to antituberculous chemotherapy in tuberculous meningitis remains controversial (Cocci, 1956; Voljavec, Orton & Corpe, 1959; Hockaday & Smith, 1966; Freiman & Geefhuysen, 1970; Osuntokun, Adeuja & Familusi, 1971; Idriss, Sinno & Kronfol, 1976, Haas *et al.* 1977). The routine use of steroids has improved survival but has also increased the incidence of neurologic sequelae (Freiman & Geefhuysen, 1970; Idriss, Sinno & Kronfol, 1976).

A study was conducted from March 1978 to March 1980 to ascertain criteria for better clinical diagnosis of tuberculous meningitis and to establish trends and patterns in both laboratory and clinical findings for better future clinical management of these patients. This study included 735 patients admitted to the Abbassia Fever Hospital (AFH, Ministry of Health, Arab Republic of Egypt) meningitis ward. A total of 100 of these 735 patients had positive CSF cultures for *M. tuberculosis*. This report is an effort to analyze pre-admission historical data, physical findings on admission, laboratory data (CSF examination, admission CBC, chest X-ray) and the clinical outcome of these 100 patients with a conclusively established diagnosis of tuberculous meningitis.

PATIENTS AND METHODS

Egyptian patients from the north-eastern section of the greater Cairo area presenting to the AFH with meningeal signs were admitted to the meningitis ward. History, physical examination and routine laboratory tests were performed. Each patient's admission condition was classified as stage 1 (awake and alert), stage 2 (drowsy but arousable), or stage 3 (comatose) as previously reported (Gordon & Parsons, 1972).

Samples of CSF were obtained on admission, hospital day 2–3, day 5–8, and then as clinically indicated. Samples were cultured on Lowenstein-Jensen media and smear examination for acid fast bacilli (AFB) was done (4–6 cc of CSF were centrifuged and the sediment was placed on three slides which were stained by the Ziehl–Neelsen method and scanned for 10 min each). On admission all patients were started on broad spectrum, parenteral antibacterial treatment (ampicillin alone or penicillin and chloramphenicol) because of the high probability of partially treated bacterial meningitis in this clinical setting.

The clinical diagnosis of tuberculous meningitis was established using a high index of suspicion; knowledge that tuberculous meningitis is frequent in this

Table 1. *Age distribution, admission status, and mortality of 100 patients with culture-confirmed diagnosis of tuberculous meningitis*

Age (years)	Number	Admission status			Mortality Number (%)
		Alert	Drowsy	Comatose	
> 1	5	—	2	3	5 (100)
1–3	18	—	4	14	15 (83)
4–9	31	—	17	14	22 (71)
10–15	13	1	7	5	10 (77)
16–25	18	1	7	10	16 (89)
> 25	15	—	7	8	11 (73)
Total	100	2	44	54	79 (79)

patient population; (Hassan & Abdel Wahab, 1969) a history of a long duration of illness before admission; admission CSF glucose, protein and cell count; and a CSF glucose level which remained low or fell after 24–48 h of adequate parenteral antibiotic treatment for bacterial meningitis. Once the diagnosis was clinically established, patients were immediately started on anti-tuberculous treatment. Isoniazid was started at 10 mg/kg daily intramuscularly (maximum 600 mg daily) and was continued for 2 years. It was given orally when the patient was alert. Ethambutol was started at 25 mg/kg daily administered orally (maximum 1200 mg daily), was decreased to 15 mg/kg daily after 42 days, and was continued for 2 years. Streptomycin was given at 15 mg/kg daily intramuscularly (maximum 1 gm daily) for 42 days and was then discontinued. This combination of antibiotics was used because of drug availability and cost. Steroids were used only when papilloedema or optic neuritis were observed. Chest X-rays were performed on 56 patients, since 44 patients died before the X-ray could be taken. Surviving patients were initially hospitalized for 6–7 months and then were observed monthly until their two-year therapy had been completed.

RESULTS

Pre-admission historical data

Fifty-one patients were males and 49 were females. Ages ranged from 2 months to 50 years, with 54% of patients under 10 years of age. The mean duration of illness before admission was 23 days. The age distribution of these patients, their condition on admission and their respective mortality rate is expressed in Table 1. It is evident that the mortality rate overall and within each age category closely paralleled the clinical condition on admission. Eighty-two per cent of patients who were comatose (stage 3) when specific anti-tuberculosis therapy was started died, while 52% of those who were drowsy (stage 2) died and neither of the 2 who were alert (stage 1) died (too few numbers in this last category makes it difficult to statistically evaluate the data). All patients appeared to come from a low socio-economic class and the majority had received antibiotic therapy prior to admission.

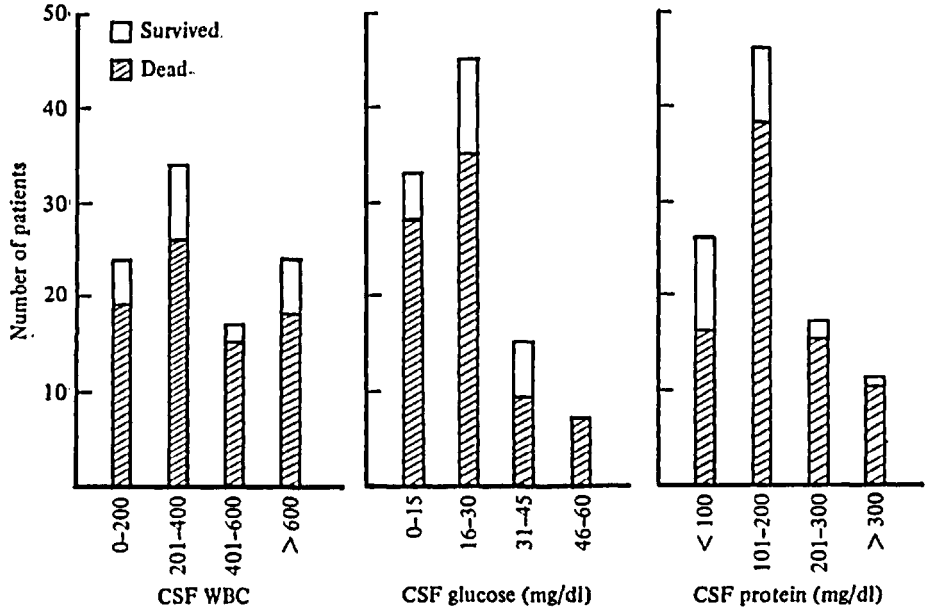

Fig. 1. White cell, glucose and protein levels in CSF in relation to survival.

Admission physical findings

Physical findings on admission included nuchal rigidity in 76 patients, paralysis of the VIth cranial nerve in 44, papilloedema in 8 and optic atrophy in 3 patients. Choroid tubercules were not seen on funduscopic examination. None of these findings were helpful in distinguishing these patients from patients admitted with subsequently determined non-acid-fast bacterial meningitis.

Clinical laboratory data

At the time of admission a CBC; bacteriological culture of blood and CSF; CSF cell count, glucose, and protein determination (Fig. 1), and CSF examination for AFB were carried out on all patients in the study. Only 2 of the 100 admission CSF samples were positive by AFB smear. No subsequent CSF samples taken from patients after admission were positive on microscopy for AFB. The mean peripheral WBC was 12404 (range 4800–27300) and the mean PMN to lymphocyte ratio was 61:31. No leukemoid reactions were noted. CSF cell counts showed a mean WBC of 531 at admission. Monthly CSF samples obtained from the 21 survivors revealed a gradual decreasing CSF pleocytosis with a mean of 101 cells at 4 months after hospitalization. Mean glucose at admission was 23 mg/dl and mean CSF protein was 166 mg/dl. CSF glucose level on a total of 65 patients was repeated 24–28 h after admission and it was found that 41 had levels equal to or less than the values obtained at admission, 15 had increases but were still below 30 mg/dl and 13 showed a mean increase of 8 mg/dl (range 6–43 mg/dl). The CSF glucose was normal at 1 month in all 21 treated, surviving patients. The CSF protein was normal by 1 month in 5 patients but remained elevated (> 150 mg/dl) for 3–4 months in 6 patients.

Bacteriological data by definition as a criteria for this study showed

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M. tuberculosis in the CSF of all patients included in this group. A total of 172 CSF samples were positive for *M. tuberculosis*, 162 were obtained before anti-tuberculous therapy was initiated and 10 obtained after initiation of anti-tuberculous therapy. These culture data were not of help in the initial diagnosis decision process.

Other laboratory and clinical findings

Chest X-rays were performed on 56 patients; 22 (39 %) were normal and 34 (61 %) were consistent with pulmonary tuberculosis. The abnormalities on chest X-ray in these 34 patients were nodular perihilar infiltrates with hilar adenopathy (16); upper lobe infiltrates, one with a cavity (7); diffuse infiltrates (4); a miliary pattern (3); lower lobe infiltrates (3); and multiple right lower lobe cavities (1). Interestingly, the mortality rate was not significantly different in those with a positive chest X-ray (55 %) than in those with normal X-ray (67 %).

Twenty-four of the 100 patients in this study died within the first 7 hospital days before a clinical diagnosis of tuberculous meningitis could be made. Fifty-three of the 76 patients administered specific antituberculous therapy died (35 within the first 10 days of therapy and 18 after more than 10 days of therapy).

Ten of the survey patients had residual neurologic sequelae at discharge; 4 had hemiparesis (2 of these 4 were also aphasic and 1 was blind); 2 were blind, 1 was myopic, 2 had VIth nerve palsies and 1 had papilloedema. Neurologic sequelae resolved in 3 patients (2 with VIth nerve palsy and 1 with papilloedema) during out-patient follow-up, while 3 had increased sequelae (1 with myopia developed grand mal seizures and 2 demonstrated marked retardation).

DISCUSSION

The clinical diagnosis of tuberculous meningitis is difficult to establish. Only a high index of suspicion will lead to early treatment which is essential for good clinical results, especially in developing countries where treatment facilities are limited.

In this series the average duration of illness before referral to a hospital was long, averaging 23 days, and as a result 54 patients were already in coma at the time of admission. There are few classic physical signs pathognomonic for tuberculous meningitis. In this series palsy of the VIth cranial nerve (present in 44 % of patients and higher than the 9·5 % incidence in patients with bacterial meningitis on this ward (Hanna *et al.* 1975)) and nuchal rigidity (76 % of patients) were indicative clinical signs. Although choroidal tubercules have been reported in patients with tuberculous meningitis (Lincoln & Sewell, 1963; Illingworth & Lorber, 1965; Bwibo, 1979) none were seen in any of these 100 patients.

Laboratory procedures may aid in supporting the clinical suspicion of tuberculous meningitis. The variability of the CSF picture is of major importance. A CSF glucose that continues to fall or does not rise after 48 h of adequate therapy for bacterial meningitis is more important than an absolute value (Tramont, 1976). The CSF glucose was falling or remained low after 24–48 h of antibiotic therapy for bacterial meningitis in 81 % of patients evaluated in this study. The AFB smear of the admission CSF was a very low-yield procedure; positive in 2 %. The chest X-ray was helpful only when positive. Other series utilizing a routine chest X-ray

as part of the diagnostic criteria had high positive rates (Voljavec, Orton & Corpe, 1959; Lincoln, Sordillo & Davies, 1960; Osuntokun, Adeuja & Familusi, 1971; Bobrowitz, 1972; Steiner & Portugaleza, 1973; Cardozo, Raidoro & Patel, 1976; Idriss, Sinno & Kronfol, 1976; Bwibo, 1979). In this series, chest X-rays were normal in 22 patients and suggestive of pulmonary tuberculosis in 34. A miliary chest X-ray pattern, said to be associated with tuberculous meningitis (Stead & Bates, 1980; Grossman & Jawetz, 1981), was present in three. The reported variability in positive admission tuberculin skin tests reflects the severity of illness and the type of tuberculin test used (Voljavec, Orton & Corpe, 1959; Lincoln, Sordillo & Davies, 1960; Steiner & Portugaleza, 1973; Cardozo, Raidoro & Patel, 1976; Naughton *et al.* 1981). Previous testing with 5 I.U. Tween-stabilized PPD on this ward revealed 29% positive in patients with subsequently positive CSF cultures for *M. tuberculosis* (unpublished data).

Mortality rates vary in reports on tuberculous meningitis (Lincoln & Sifontes, 1953; Lorber, 1954; Weiss & Flippin, 1965; Hassan & Abdel Wahab, 1969; Osuntokun, Adueja & Familusi, 1971; Steiner & Portugaleza, 1973; Escobar *et al.* 1975; Visudhiphan & Chiemchanya, 1975; Idriss, Sinno & Kronfol, 1976; Kennedy & Fallon, 1979), reflecting basic health and nutrition of the population studied, patient age, severity of illness at the time of presentation for care, delay in starting anti-tuberculous therapy, and standards used to diagnose tuberculous meningitis. All patients in this series had laboratory confirmed tuberculous meningitis. The severity of illness at the time of hospitalization was extreme, with 54 patients presenting in coma. The mortality rates in each age group reflected the comatose rates. The patient's condition at the time of starting treatment was an important factor in predicting mortality; 82% who were comatose died and 52% of those who were drowsy died. The mortality rate was 46% for patients surviving for 10 days of antituberculous therapy and 30% for those surviving for 20 days of therapy. All five patients under 1 year of age died. There were no spontaneous recoveries among the 24 patients with *M. tuberculosis* positive CSF cultures who were not clinically diagnosed and treated, in contrast to reports of this phenomenon (Edmond & McKendrick, 1973). Patients with lower initial CSF proteins had higher survival rates. Ten of 21 survivors (48%) had neurologic sequelae.

Tuberculous meningitis has a wide range of clinical and laboratory presentations. Physicians must be aware of this fact considering the diagnosis. Tuberculous meningitis should be considered in any patient with a slowly progressive CNS presentation or CNS signs with VIth nerve palsy. Suggestive laboratory findings are a persistently low CSF glucose and an abnormal chest X-ray. Absence of choroidal tubercles, a negative CSF AFB smear, a normal chest X-ray, or a negative PPD skin test do not exclude the possibility of tuberculous meningitis. The patient must seek medical consultation early in the clinical course and the physician must initiate appropriate therapy based on clinical suspicion when the patient is still awake and alert in order to reduce mortality and morbidity.

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