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Emergence of Tuberculous Meningitis in Egypt as an Important Public Health Problem During a Five-Year Surveillance (1998-2003)

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Abstract: Tuberculous meningitis, one of the most common chronic infections of the central nervous system, had emerged as a significant cause of meningitis in Egypt. In this study we assess the epidemiology, clinical characteristics, mortality and laboratory features of tuberculous meningitis in patients during the enhanced meningitis surveillance 1998-2003. Retrospectively, we reviewed the data of 134 immunocompetent patients with culture positive *Mycobacterium tuberculosis* infection. The overall case fatality rate for patients with tuberculous meningitis was 47%. It was significantly higher ($p<0.001$), than that for all other causes of bacterial meningitis (21.3%). The median age of cases was 23 years. They were 49.6% males and 57.5% of cases occurred in patients>20 years of age. The characteristic cerebrospinal fluid findings, included moderately elevated leucocytes count (median: 175 mm^{-3}), decreased glucose (median: 30 mg dL^{-1}), elevated protein (median: 105 mg dL^{-1}) and proportion of lymphocytes % (median: 30). Patients had long prodromal period>5 days (65%) and low or moderate grade fever (= 38°C) was found in 70%. Tuberculous meningitis has emerged as a significant cause of bacterial meningitis in Egypt. Rapid diagnosis and earlier initiation of therapy is important to avoid the high risk of mortality or disabling neurologic sequelae.

Key words: Mycobacterium tuberculosis meningitis, epidemiology and clinical features of TBM, TBM in Egypt, clinical and laboratory features of TBM

INTRODUCTION

Mycobacterium Tuberculosis Meningitis (TBM) is a life-threatening form of tuberculosis and is the most common form of central nervous system infection (Katti, 2001). The disease is less common in developed countries but is a serious cause of mortality and morbidity in developing nations (Meyers, 1985; Gracey, 1988; Sutlas *et al*., 2003). Meanwhile, the incidence of TBM in a community is directly proportional to the prevalence of tuberculous infection in the general population, which in turn is dependent on the socioeconomic conditions of the community (Sutlas *et al*., 2003). TBM occurs in approximately 7-12% of patients with pulmonary tuberculosis (Molavi, 1985). On the other hand clinical diagnosis of TBM is difficult and discrimination of cases from those of bacterial meningitis by clinical features alone is often impossible. Diagnosis of TBM in developed countries is often made after a substantial delay (Shankar *et al*., 1991). The laboratory methods remain inadequate or inaccessible in most developing countries (Joosten *et al*., 2000). In spite of the advent of new neuroimaging techniques and rapid diagnostic tests for TBM (Thwaites *et al*., 2002) the diagnosis can be difficult and delayed, increasing the morbidity and mortality (Mak *et al*., 1998; Leonard and Prez, 1990). The mean time for detection of *M. tuberculosis* is about 12 days (Dirra *et al*., 2003). The mortality rate represented in different studies varied from 20 to 50% and of the survivors 20-30% was left with permanent neurological sequelae (Idris *et al*., 1976; Girgis *et al*., 1991). The high mortality rate is due to the fact that the clinical presentation of TBM is notoriously variable, making the clinical diagnosis of the disease a problem (Alvarez and McCabe, 1984). Recently we have found simple parameters can be used for early diagnosis of TBM (Youssef *et al*., 2006).

To date, a paucity of literatures are available regarding TBM in Egypt. The last reporting was conducted in 1996 (Girgis *et al*., 1998) and in this study we describe the epidemiology, clinical, morbidity, mortality and laboratory diagnosis, of TBM patients identified during the recent sentinel surveillance for meningitis in Egypt.

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MATERIALS AND METHODS

Surveillance system: TBM was evaluated as part of an ongoing surveillance of meningitis, during 5-year period (1998-2003), in a network of twelve infectious disease hospitals located throughout Egypt (Alexandria, Imbaba, Abbassia, Assiut, Aswan, Mehalla, Shebin El Kom, Zagazig, Port Saeid, Fayiom, Quena and Benha). The meningitis surveillance was a collaborative project among the Ministry of Health and Population (MOHP), US Naval Medical Research Unit No 3 (NAMRU-3), Centers for Disease Control and Prevention (CDC) and Field Epidemiology Training Program (FETP). All patients with possible meningitis had a standard clinical, demographic and laboratory evaluation. Surveillance data included in this series were obtained with informed consent either from patients or from their parents or guardians.

Case definition: Any suspected case with fever, stiff neck and/or bulging fontanel in infants, or having White Blood Cell (WBC) count of CSF = 10 WBCs mm^{-3} was enrolled in the surveillance system. While suspected cases of TBM were enrolled based on, the medical history of pulmonary TB, cranial nerve palsy, poor response to bacterial therapy for 48 h, abnormal mental status, chest radiographs performed on admission whenever feasible and CSF findings (high protein, low glucose and moderately elevated WBC). The final diagnosis of TBM was classified as definite culture of CSF yielded *M. tuberculosis.*

Laboratory methods: Lumbar puncture was performed on all suspected cases and CSF specimens were obtained and processed with standard methods including Gram stain, normal bacterial culture and specific culture for *M. tuberculosis*, on Lowenstein Jensen's media.

In addition CSF cell counts and differential leukocyte counts were determined microscopically. CSF was tested for glucose and total protein concentration.

Statistical analysis: Data were analyzed using computer software Epi info Ver 6.04, (CDC, Atlanta, GA). A v2 test and t test were used to test for statistical association and $p<0.05$ was considered significant. For the univariate analysis, cutoff points were determined based on the 50th percentile.

RESULTS AND DISCUSSION

Over the 5-year study period (1998-2003), a total of 10400 patients were enrolled in the meningitis surveillance network. Of those, 943 (9%) had culture confirmed bacterial meningitis, of whom 134 patients (16%) had TBM and 809 (84%) non TBM with other bacterial meningitis, 35% *Streptococcus pneumoniae*, 20% *Neisseria meningitides,* 3% *Haemophilus influenza* and 23% other bacteria (Fig. 1). The diagnosis of all TBM cases was confirmed mainly by the culture of the CSF. Ziehl-Nelson staining was positive only in 2 patients, out of 40 patients (5%). The TBM cases<5 years were 16.4%, while cases = 5 years were 83.6% (Fig. 2). All patients were hospitalized for diagnosis and initial treatment. All patients were negative for human immunodeficiency virus with no other underlying disease. The median length of hospitalization was 8 days (range 1-92 days). There were 49.6% males and 50.4% females. About 45% of TBM patients have been treated with empirical antibiotic before admission.

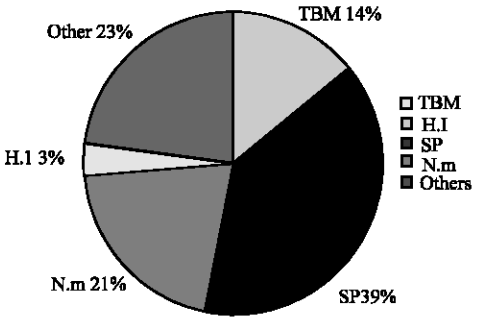

Fig. 1: Etiology of bacterial meningitis from hospitals in Egypt (1998-2003)

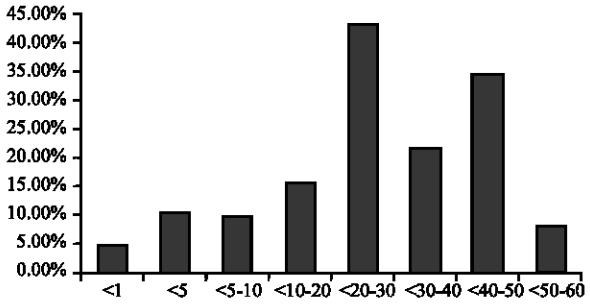

Fig. 2: Age distribution in patients with TBM (1998-2003)

TBM occurred in all age groups with a median age of 23 years (range 5 months to 56 years). It was a third of infections (32%) detected in young adults (21-30 years), while (58%) occurred in patients>20 years (Fig. 2). The overall Case Fatality Ratio (CFR) for patients with TBM (47%), was significantly higher ($p<0.001$) than that for all other causes of bacterial meningitis (21.3%). The CFR is high (50%) in age group<5 years, moderate (37%) in age group 21-30 years, but very high (65%) in age group> 30 years old (Fig. 3). The permanent neurological sequelae

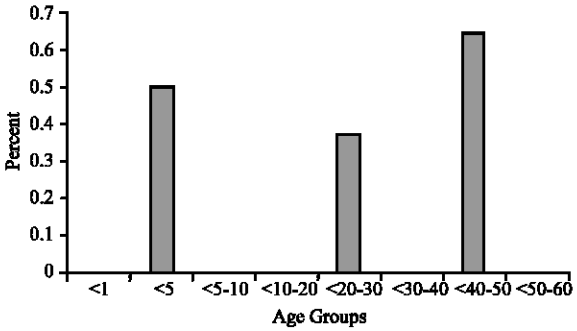

Fig. 3: Mortality in patients with TBM in different age groups (1998-2003)

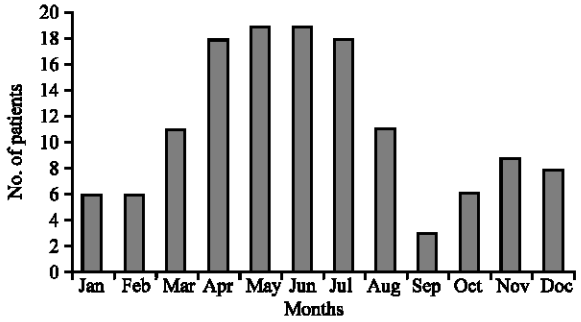

Fig. 4: Cumulative monthly enrollment of TBM patients (1998-2003)

Table.1: Clinical characteristics and Case Fatality Rate (CFR) in TBM positive patients (1998-2003)

Characteristics	Cases of TBM (134)
Median age (years) and range	23 (5 month- 56 y)
Males (%)	53
CFR (%)	47.0
Median length of hospitalization and range (days)	8.0 (1-92)
Prodromal period and range (days)	12 (0-95)

Table. 2 Important laboratory, clinical parameters and % of TBM in Egypt

Diagnostic parameters	% TBM (134)
Interval > 5 days	65
WBC =1000	93
Lymphocyte = 30%	28
Protein = 100 mg dL^{-1}	55
Glucose = 40 mg dL^{-1}	59
Temperature = 38.5 °C	70

were seen in 8/60 (13%) of surviving patients. Hydrocephalus and optic atrophy were the most frequent sequelae. Prodromal period prior to admission was much longer in the TBM cases (mean 12 days, range 0-95 days) than non TB cases (Table 1). Among patients who survived, the mean length of hospitalization was 18 days, range 1-92 (Table 1). About 72% of cases were admitted during the months of March, April, May, June, July and August (Fig. 4).

Clinically, the most common presenting symptoms and signs present on admission were 81% headache, 75% stiff neck, 70% low or moderate grade fever (= 38°C), 69% nausea and vomiting and 26% seizures. In addition, 52% had associated lung pathology (nodular perihilar, lober and diffuse infiltrate) on a chest X-ray. The characteristic CSF findings are shown in Table 2. The WBC count = 1000 were found in 93%, protein level of = 100 mg dL^{-1}, was found in 55% and the majority (59%) had a glucose level of = 40 mg dL^{-1}. In addition the lymphocyte predominance >30% was found in 28% of cases.

Surveillance of TBM has been expanded, for a first time throughout Egypt to have representative data for the country and to give more accurate picture of diseases. It is being transitioned into routine communicable disease surveillance program for MOHP. The development of this surveillance network has provided important public health information to MOHP. With enhanced surveillance and diagnostic capabilities, TBM has emerged as a significant cause of bacterial meningitis in Egypt and represents the 2nd leading cause of culture positive CSF in children <5 years age group (Youssef *et al*., 2004). Patients with TBM are usually present with longer history (prodromal stage), since TBM is a chronic disease and their CSF are frequently clear, with moderate numbers of leukocytes, in combination with an increased protein concentration and a low glucose.

Usually the lack of specific symptoms and signs in patients with TBM makes early diagnosis of TBM difficult (Kumar *et al*., 1999) and associated with a high morbidity and mortality if there is a delay in diagnosis (Seth and Sharma, 2002). This type of presentation is responsible for much of the initial diagnostic confusion. On the other hand, the diagnosis of TBM has been a problem because various clinical manifestations can be confused with those of other causes of the central nervous system infections i.e., neurocystic cercosis, neurobrucellosis and cryptococcal meningitis (Katti, 2001). In addition atypical CSF findings may add to the difficulties of diagnosis in the form of neutrophil predominance, acellular or even normal CSF (Kaarstaed *et al*., 1998).

Meanwhile the newer diagnostic tests are unlikely to be available in many developing countries (Dirra *et al*., 2003). These difficulties lead many investigators to depend on clinical and rapid laboratory results and or the radiological investigations (Thwaites *et al*., 2002; Seth and Sharma, 2002; Kaarstaed *et al*., 1998; Paganini *et al*., 2000; Pagliano *et al*., 2000). In additions, different methods have been known and reported for TBM diagnosis either for adults or children (Alvarez and McCabe, 1984; Youssef *et al*., 2006; Faella *et al*., 2006; Yaramis *et al*., 1998; Hosoglu *et al*., 1998, 2003).

Despite the introduction of new and potent anti-tuberculous drugs, the mortality with TBM remain overall high (47%) and very high in older patients >30 years (65%) and was associated with increased mean length of hospitalization (8.0 days, range 1-92). These indicate that the prevalence of TB is high in Egypt and shall be considered a major health problem (Youssef *et al*., 2004).

Meanwhile the increase in TBM admissions during the months of March to August (Fig. 2) may be due to the fact that some viral infections such as influenza, measles and mumps are very common during the months of February, March and April causing a decrease in immunity, thus the chance for dissemination of mycobacteria is greater (Girgis *et al*., 1998). The admission CSF findings in the majority of patients with TBM are that of subacute lymphocytic meningitis (21%) with a decrease in glucose (44%) and raised protein (41%) as reported before (Verdon *et al*., 1996). However in a number of patients the CSF findings are not consistent with that of subacute lymphocytic meningitis due to a predominance of polymorphonuclear cells and a mild decrease in glucose content (Girgis *et al*., 1998). We found that (>70%) of patients with TBM had a predominant (50%) polymorphonuclear type of CSF on admission. This is much higher than reported before (Alvarez and McCabe, 1984) but more close (70-80%) to what reported by others (Girgis *et al*., 1998).

CONCLUSION

TBM continues to be a significant public health problem in Egypt. The emergence of TB as a major cause of meningitis is particularly concerning in light of the high mortality. However, increased clinical awareness of TBM is critical for early diagnosis and initiation of antituberculous therapy to reduce the high mortality associated with this condition. Additional studies should be conducted to better understand risk factors for TBM in Egypt and the high mortality associated with it.

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