Evaluation of tuberculosis meningitis within the last twenty years in Iran

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Abstract: Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis (TB) and has very high morbidity and mortality. TBM is typically a subacute disease with symptoms that may persist for weeks before diagnosis. This study evaluated those patients hospitalized with tuberculosis meningitis within the last twenty years in Tabriz, Iran. This descriptive analytical study evaluated all patients hospitalized with tuberculosis meningitis during twenty years. The patients were divided into adults and children groups. The study was conducted on 71 adults and 21 children. Required information including age, gender, main complaint, other symptoms of the disease, duration of the symptoms onset before hospitalization, records of close contact, records of vaccination for children were collected using characterization sheets. Mean age of the patients was 30.12 ± 6.14 years, respectively. Considering physical examination, neck rigidity, Kernig sign, and Brudzinski's sign were respectively the most common ones. The disease was more prevalent in younger-than-4-years old children and young adults. Meningitis, TB meningitis, mal-treated meningitis, and viral meningoencephalitis were regarded as the most common primary detections among adults and TB meningitis, mal-treated meningitis, and bacterial meningitis among children. This study demonstrated descending process of tuberculosis meningitis incidence at infectious disease wards of adults and children (within the last twenty years).
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Introduction

Tuberculous meningitis is Mycobacterium tuberculosis infection of the meninges the system of membranes which envelops the central nervous system. It is the most common form of CNS tuberculosis.(Golforushan F, Azimi H, Goldust M, Sadeghi M, Yousefi N 2010; Peonim, Sujirachato, Srisont, Udnoon 2012; Principi, Esposito 2012) Tuberculous meningitis (TBM) develops in 2 steps. *Mycobacterium tuberculosis* bacilli enter the host by droplet inhalation. Localized infection escalates within the lungs, with dissemination to the regional lymph nodes. In persons who develop TBM, bacilli seed to the meninges or brain parenchyma, resulting in the formation of small subpial or subependymal foci of metastatic caseous lesions, termed Rich foci.(Chen, Wang, Zeng et al. 2012; Heizchi Qadim H, Golforoushan F, Azimi H, Goldust M 2013; Ho Dang, Le Thi, Wolbers et al. 2012) The second step in the development of TBM is an increase in size of a Rich focus until it ruptures into the subarachnoid space. The location of the expanding tubercle (ie, Rich focus) determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space cause meningitis.(Hristea, Olaru, Baicus, Moroti, Arama, Ion 2012; Saleh P, Bastam P, Piri R, Goldust M, Naghavi-Behzad M 2013; Singh, Garg, Singh et al. 2012) Currently, more than 2 billion people are infected with tuberculosis (TB), of which approximately 10% will develop clinical disease. The incidence of central nervous system (CNS) TB is related to the prevalence of TB in the community, and it is still the most common type of chronic CNS infection in developing countries.(Kalita, Prasad, Maurya, Kumar, Misra 2012; Salehi R, Ghaffari S, Abbasnezhad M, Goldust M 2009; Tu, Vu, Rozenbaum, Woerdenbag, Postma 2012) Diagnosis of TB meningitis is made by analysing cerebrospinal fluid collected by lumbar puncture. The CSF usually has a high protein, low glucose and a raised number of lymphocytes. Acid-fast bacilli are sometimes seen on a CSF smear, but more commonly, M. tuberculosis is grown in culture.(Dramowski, Morsheimer, Jordaan, Victor, Donald, Schaaf 2012; Salehi R, Parvizi R, Ansarin K, Imani S, Goldust M 2013; Xiao, Sun, Wu et al. 2012) A spiderweb clot in the collected CSF is characteristic of TB meningitis, but is a rare finding. ELISPOT testing is not useful for the diagnosis of acute TB meningitis and is often false negative, but may paradoxically become positive after treatment has started, which helps to confirm the diagnosis.(Harris, Lindsley, Henchaichon et al. 2012; Yadav, Parihar, Agrawal, Bhatele 2011) More than half of cases of TB meningitis cannot be confirmed microbiologically, and these patients are treated on the basis of clinical suspicion only. The culture of TB from CSF takes a minimum of two weeks, and therefore the majority of patients with TB meningitis are started on treatment before the diagnosis is confirmed.(Garg,

Paliwal, Malhotra 2011; Lumb, Bastion, Carter, Jelfs, Keehner, Sievers 2011) Imaging studies such as CT or MRI may show features strongly suggestive of TB meningitis, but cannot diagnose it. The treatment of TB meningitis is isoniazid, rifampicin, pyrazinamide and ethambutol for two months, followed by isoniazid and rifampicin alone for a further ten months. Steroids are always used in the first six weeks of treatment (and sometimes for longer).(Abreu, Gonzalez, Gonzalez et al. 2011; Goldust, Rezaee, Hemayat 2012; Shao, Xia, Zhu et al. 2011) Treatment must be started as soon as there is a reasonable suspicion of the diagnosis. Treatment must not be delayed while waiting for confirmation of the diagnosis. This study evaluated the tuberculous meningitis in last twenty years in Iran

Methods

This descriptive analytical study evaluated all patients hospitalized with tuberculosis meningitis at infection wards of Emam Reza hospital, Tabriz from Dec., 1992 to Dec., 2012. The patients were divided into adults and children groups. The adults group was consisted of 74 patients and the children group was consisted of 24 patients. Three children and 3 adults were excluded due to incompleteness or unavailability of their files. Finally, this comparative study was conducted on 71 adults and 21 children. This study was approved by ethic committee of Tabriz university of medical sciences. Written consent was obtained from all the patients and their parents. Required information including age, gender, main complaint, other symptoms of the disease, duration of the symptoms onset before hospitalization, records of close contact, records of vaccination for children were collected using characterization sheets completed by residents of infection and children wards when the patients were hospitalized. Date of hospitalization, date of release from hospital or date of death inserted in hospital admission files are used to evaluate the patients' residence. Unfortunately, although tuberculin test was conducted on most patients, its results have only been recorded in files of 44% of adults and 52% of children. Therefore, the test and its quantitative results have been evaluated only in those patients whose test result was read and registered after 48-72 hours. Paraclinically, quantitative amounts of Hb, WBC, ESR, Na+, K+, urea, and creatinine were extracted from test reports related to the hospitalization day. CSF obtained from the patients when they were admitted was regarded as criterion of CSF biochemical and cytological analysis and its bacteriology obtained through standard methods. To evaluate mycobacterium traces of tuberculosis, CSF in all cases, and sometimes, mucus, stomach excretions, and urine were microbiologically studied in adults. The studies included CSF and stomach excretions in all children. The results were recorded in the files (averagely, in three times). Meanwhile, centrifuged sediments of CSF and Ziehl-Neelsen staining were used to prepare smear from CSF. Lowenstein-Jensen medium was used to culture it. Radiologic reports found in the patients' files were used as criterion to judge about CR and results of skull radiography (in children). Unfortunately, most patients underwent CR only once when they hospitalized. There were results of EEG and cerebral CT-scan, and in some cases, CT-scan cliché in the files. Patients CR results as well as pathological sheets found in the patients' files were used as criteria to judge about simultaneous extensive CNS tuberculosis. Positive results obtained from microbiological and pathological evaluations were used to diagnose the problem in 15% of adults and 19% of children. In the rest cases, the disease was detected whether through relying on a set of clinical and epidemiological evidences especially any records of close contact, PPD test results, evidences on simultaneous extensive CNS tuberculosis, results of paraclinical studies including CR, and biological and cytological analysis of CSF or relying on strong detective presumption and appropriate clinical response to treatment tests. Type of anti-TB treatment regime at the beginning of treatment stage and prescription or non-prescription of corticosteroid and how to use them were extracted from medical prescriptions of the files. The resulted complications during hospitalization were evaluated based on progress notes and variations in medical prescriptions.

Statistical analysis

SPSS^{TM}, version 16 is the used statistical software program. Chi-square test was used to evaluate mean comparisons and Mann-Whitney-U test was applied to study the relationship between rank and qualitative variables. The resulted outcomes stated as frequency percentage, mean along with standard deviation and $p<0.05$ was regarded as the meaningful level.

Results

Mean age of the patients was 30.12 ± 6.14 years and the youngest and oldest patients were 13 and 60 years old, respectively. Also, 42% of the adult patients included 12-20 years old patients. In children group, the youngest and oldest patients were 21 months and 12 years old with the mean age of 6.24 ± 1.34 years, respectively. Additionally, 38% of children were younger than 4 years old. There were 31% male and 69% female patients in adults and 43% male and 57% female cases in the children groups. This study demonstrated descending process of tuberculosis meningitis incidence at infectious disease wards of adults and children (within the last twenty years). In this study, more than 50% of the understudy children did not effectively vaccinated. This study demonstrated

that, the symptoms onset is more common during 1-2 weeks before hospitalization in both adults and children groups. It was 20 and 23 days in adults and children, respectively. The chief complaints have been described in tables 1 based on their prevalence among adults and children. Considering physical examination, neck rigidity, Kernig sign, and Brudzinski's sign were respectively the most common ones. Table 2 refers to prevalence of physical findings among adults and children. The disease was more prevalent in younger-than-4-years old children and young adults. Females were more affected by the disease in both groups such that males ratio to females was 0.45 and 0.75 among adults and children. In this study, 10% of adults and 33% of children previously experienced close contact with bacilifer persons and 52% of children were whether non-vaccinated or received ineffective vaccination. Mean duration of the disease onset was 20 and 23 days before hospitalization and mean duration of hospitalization was 36 and 33 days for adults and children, respectively. Meningitis, TB meningitis, mal-treated meningitis, and viral meningoencephalitis were regarded as the most common primary detections among adults and TB meningitis, mal-treated meningitis, and bacterial meningitis among children. Variation and reduction of conscious level were found as the most common chief complaint at both groups. Headache, vomiting, and fever in adults and vomiting, fever, and drowsiness among children were the most common symptom and neck rigidity, Kernig sign and Brudzinski's sign were the most common physical finding. Also, PPD+ was seen in 42% of adults and 36% of children and there was nerve VI paralysis in 17% of adults and 33% of children as the most prevalent neural focal damage. Papilledema was seen in 30% of adults and 29% of children. There was abnormal CR in 56% of adults and 45% of children, simultaneous CNS external involvement in 27% of adults and 14% of children, and hydrocephaly in 34% of adults and 57% of children (found through CT-scan). In this study, there was anemia in 14% of adults and 19% of children, normal range of WBC in 77% of adults and 48% of children, normal ESR in 41% of adults and 40% of children, hyponatermia in 34% of adults and 19% of children, and CRP+ in serum of 40% of adults and 65% of children. Mean ESR during the first hour was 33 and 32 in adults and children, respectively. CSF analysis referred to glucose<40, 100-500mg/dl protein, and 100-500 cells as the most common finding. There was lymphocyte superiority in the first LP in 73% of adults and 62% of children. In comparison with adults, children referred to physician at more advanced stages of the disease such that recovery rate was 100% in both groups at stage I, 89% in adults and 60% in children during stage II, 58% in adults and 33% in children at stage III. Simultaneous extra CNS involvement or milliary tuberculosis did not affect our patients' prognosis. There was a direct relationship between undesirable prognosis and CSF abnormality rate among children. However, there was not found such relationship at adults group. Mortality rate of our patients was 14% and 48% at the adults and children group, respectively.

Discussion

TBM is typically a subacute disease. In one seminal review, symptoms were present for a median of 10 days (range, one day to nine months) prior to diagnosis. A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may persist for a few weeks, after which patients can then develop more severe headache, alteredmental status, stroke, hydrocephalus, and cranial neuropathies.(Cruz, Ong, Starke 2011; Mauro, Cavalcanti, Ledonne, Giraldi, Sperli 2012) The clinical features of TBM are the result of basilar meningeal fibrosis and vascular inflammation. The clinical features of TBM are the result of basilar meningeal fibrosis and vascular inflammation.(Ambekar, Dwarakanath, Chandramouli, Sampath, Devi, Pandey 2011; Wang, Huang, Zhang, Zhu, Yang, Xu 2011) Classic features of bacterial meningitis, such as stiff neck and fever, may be absent. When allowed to progress without treatment, coma and death almost always ensue. In survivors of TBM, neurologic sequelae may occur that include mental retardation in children, sensorineural hearing loss, hydrocephalus, cranial nerve palsies, stroke-associated lateralizing neurological deficits, seizures, and coma.(Fukushima, Shiobara, Shiobara et al. 2011; Park, Hong, Lee, Koh, Kim 2011) The diagnosis of TBM can be difficult and may be based only on clinical and preliminary cerebrospinal fluid (CSF) findings without definitive microbiologic confirmation. Certain clinical characteristics such as longer duration of symptoms (>six days), moderate CSF pleiocytosis, and the presence of focal deficits increase the probability of TBM.(Che, Antoine 2011; Vidhate, Singh, Garg et al. 2011) Timely treatment dramatically improves the outcome of TBM. Thus, empiric treatment is warranted when clinical features and CSF findings are suggestive of TBM even before microbiologic confirmation.(Cunha, Hage, Nouri 2012; Kusum, Aman, Pallab et al. 2011) The recommended treatment regimen for presumed drug susceptible. TBM consists of two months of daily INH, rifampin (RIF), pyrazinamide (PZA), and either streptomycin (SM), or ethambutol (EMB), followed by 7–10 months of INH and RIF.(Nagdev, Kashyap, Parida et al. 2011; Vinnard, Winston, Wileyto, MacGregor, Bisson 2011) Prognosis of TBM largely depends on neurologic status at the time of presentation, and time-to-treatment

initiation. While the course of TBM is generally not as rapid or fulminant as meningitis due to pyogenic bacteria, empiric treatment should be initiated as soon as the diagnosis is suspected as any delay in treatment can worsen outcome. Various case series indicate a mortality rate of 7%–65% in developed countries, and up to 69% in underdeveloped areas.(de Almeida, Boritza, Cogo et al. 2011; Gunal, Yang, Agarwal, Koroglu, Arici, Durmaz 2011) Mortality risk is highest in those with comorbidities, severe neurologic involvement on admission, rapid progression of disease, and advanced or very young age. Neurologic sequelae occur in up to 50% of survivors.(Christensen, Andersen, Thomsen, Andersen, Johansen 2011; Mullan, Steenhoff, Draper et al. 2011).

Table 1. Chief complaints in understudy patients

Complaint	Adults N (%)	Children N (%)	
Decrease of conscious level	24 (34)	12 (56)	
Headache + vomiting	23 (32)	1 (5)	
Headache + fever	7 (10)	1 (5)	
Headache	4 (6)	0 (0)	
Ague and perspiration	4 (6)	0 (0)	
Headache+ drowsiness	3 (4)	0 (0)	
Restless	3 (4)	0 (0)	
Fever + vomiting	2 (3)	1 (5)	
Stomachache + amenorrhea	1 (1)		
Fever + convulsion	0 (0)	4 (19)	
Decrease of conscious level + convulsion	0 (0)	1 (5)	

Table 2. Comparison of prevalence of physical findings in adults and children

Physical findings	Adults (%)	Children (%)
Neck rigidity	61 (86)	17 (81)
Kernig sign	50 (70)	14 (67)
Brudzinski's sign	45 (63)	14 (67)
Fever >37.8	40 (56)	11 (52)
Cranial nerve paralysis	24 (35)	10 (48)
Stupor-coma	19 (27)	7 (33)
Bilateral hydiasis with decrease of light reflex	12 (17)	5 (24)
Hemiplegia	6 (8)	3 (14)
DTR↓	5 (7)	5 (24)
DTR↑	3 (4)	2 (10)
Hepatomegaly		

Conclusion

Meningitis is the most deadly form of TB. Early diagnosis and treatment can dramatically reduce the high mortality associated with this disease.

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