Cranial Nerve Palsy as a Factor to Differentiate Tuberculous Meningitis from Acute Bacterial Meningitis

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Abstract- Tuberculous meningitis (TBM) and acute bacterial meningitis (ABM) cause substantial mortality and morbidity in both children and adults. Identification of poor prognostic factors at patient's admission could prepare physicians for more aggressive monitoring of patients with meningitis. The objective of this study was to determine the predictive value of neurological features to differentiate ABM and TBM. A retrospective study was conducted between patients affected with ABM or TBM admitted to three teaching hospitals during the last 14 years in Zahedan the central city of Sistan and Balouchestan province (Iran). The neurological features include seizure, level of consciousness, stroke, focal neurologic deficit and cranial nerve palsy at the time of admission. Mean age for patients with TBM and ABM were 41 ± 22.4 and 24 ± 18.5 years respectively. In univariate analysis, all measured variables revealed significant difference between ABM and TBM patients except for seizure episodes. Multivariate logistic regression analysis showed positive predictive effect of cranial nerve palsy (AOR=1.980, CI 95%: 1.161-3.376) on the diagnosis of TBM. In our study cranial nerve palsies was the most important neurological predictor factor to differentiate TBM from ABM.

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Introduction

The hallmark signs of meningitis are sudden fever, severe headache, and a stiff neck but encephalitis is characterized by seizures, stupor, coma, and related neurological signs. Identification of poor prognostic factors at patient's admission could prepare physicians for more aggressive monitoring of patients with meningoencephalitis. Tuberculous meningitis (TBM) and acute bacterial meningitis (ABM) cause substantial mortality and morbidity in both children and adults. The mortality associated with meningitis remains high, and one of the strongest clinical factors for an unfavorable outcome is loss of consciousness (1). Besides that some other neurological signs such as seizure and focal neurologic deficit are also alerting at the time of hospitalization.

Seizure is one of the clinical feature or complication of meningitis. In the first few days of bacterial meningitis, seizures occur in about 25% of children and in more than 30% of adults with pneumococcal meningitis. Inflammation and bacterial toxin accumulation in the subpial space may cause generalized seizures, depressed level of consciousness and cranial nerve palsies, earlier in the course of infection. With the progression of inflammation and thrombosis of the meningeal veins, focal neurologic deficits including focal seizures and stroke will occur (2). In a case review on community-acquired meningitis at Massachusetts General Hospital, 23% of patients had seizure and its occurrence within 24 hours of presentation was a risk factor for death among patients with single episodes of community-acquired meningitis (3). Those neurological signs are not only poor prognostics earlier in the duration of the illness but also they have unfavorable outcome later on the follow-up period. Cranial nerve palsy (OR=2.6), hemiparesis and/or focal weakness (OR=9.3), hemiplegia and/or multiple neurological deficit (OR=7.1) and drowsiness (OR=4.2) were demonstrated to be independent predictors of neurological sequelae at six months follow-up of TBM patients in Turkey (4). Nevertheless,

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the objective of this study was to demonstrate the predictive value of the neurological signs/symptoms to differentiate ABM from TBM.

Materials and Methods

A retrospective study was conducted between patients affected with ABM or TBM admitted to three university hospitals during the last 14 years (March 1996 to June 2010) in Zahedan the central city of Sistan and Balouchestan province (South Eastern part of Iran). Those hospitals admit referred patients from all over the province with more than 2,000,000 inhabitants. Data were gathered electronically and entered into the case sheets. The diagnosis of TBM was based on a combination of clinical criteria, laboratory findings and response to treatment. Those included the presence of signs and symptoms of chronic lymphocytic meningitis, with cerebrospinal fluid (CSF) lymphocytic pleocytosis, increased proteins and decreased glucose plus a history of contact with another individual with tuberculosis (TB), TB in other organs, positive smear for acid fast bacilli (AFB), positive CSF culture for *Mycobacterium tuberculosis* and/or from other body fluids, positive CSF PCR based on detecting a 123-bp DNA segment belonging to insertion sequence IS6110 specific for *M. tuberculosis* or a response to specific anti-TB treatment (5-6). Patients were considered to have ABM if the CSF culture was positive for a bacterial pathogen or the CSF had pleocytosis with decreased glucose (less than 50% of simultaneous blood glucose) and the patient had a good response to antibiotics without receiving anti-TB treatment. A total of 358 patients were registered and their information was extracted using a standard questionnaire (Figure1). Sixty-three patients were excluded because they had incomplete data to reach a definite diagnosis. We classified patients as 'definite or highly suggestive TBM' patients if there was a positive CSF smear and/or culture and/or PCR for acid-fast bacilli or *M. tuberculosis*. If clinical, laboratory and radiological features suggested TBM but the smear, culture or PCR were negative for bacilli, these patients were regarded as 'probable TBM' cases. The diagnostic criteria for the latter group were CSF profile typically seen in TBM with one or more of the following: 1) TB in other organ (lung, spine, pleura, peritoneum and lymph node); 2) family history of TB, radiological features suggestive of TBM and/or good response specifically to anti-tuberculosis treatment. Sixty-three patients were excluded because they had incomplete data to reach a definite diagnosis, while 109 had proven TBM and 186 had proven ABM. We classified 36 patients as definite TBM (smear and/or culture and/or PCR positive) and the remaining 73 cases as probable TBM. The clinical severity of TBM at the time of admission to the hospital was graded following the UK Medical Research Council classification (stage 1: fully conscious and rational without focal signs; stage 2: lethargy, altered behavior, meningismus or minor focal signs; and stage 3: stupor, coma, or a severe focal neurological deficit) and the Glasgow coma score (4,7). Cranial CT scans, lumbar puncture, chest X-rays, blood cell counts, erythrocyte sedimentation rate (ESR) and purified protein derivative (PPD) skin tests (5 tuberculin units) were performed in all cases. Patients initiating anti-TB treatment received isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and rifampicin for 8-10 months. Corticosteroids were administered to patients with TBM in stages 2 and 3 and ventriculoperitoneal shunts were inserted in patients with raised intracranial pressure as appropriate. The characteristics of patients including seizure, level of consciousness, focal neurologic deficit and cranial nerve deficit at the time of admission with proven TBM were compared to patients with ABM using univariate analyses. Variables statistically significant at the univariate level using Chi-squared or student's t-tests were entered into a logistic regression model using forward elimination procedures in SPSS software, version 17.0 to identify diagnostic predictors. Odds ratios and 95% confidence intervals were used to quantify the strength of these associations.

Results

Totally 295 patients were entered into the study in which 186 patients recognized as ABM and 109 as TBM (Figure 1). The mean age of ABM and TBM patients were 24 ± 18.5 and 41 ± 22.4 years respectively ($P<0.001$). The median of disease duration for ABM and TBM patients were 3 and 15 days, respectively which showed significant difference. Male sex was more prominent in ABM cases comparing to TBM patients ($P=0.017$). Distribution of neurological factors was demonstrated in table 1. Mean age for patients with stroke after getting TBM or ABM were 42.8 ± 10.4 and 27.6 ± 9.9 years, respectively. Primary and secondary generalized epileptic phenomena were more common in both groups but the difference between two groups was not statistically significant.

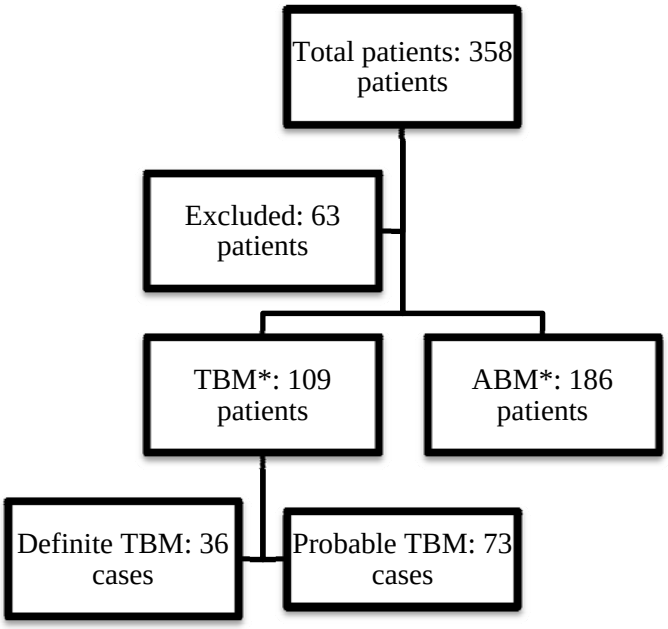

Figure 1. Clinical profile.

*TBM: Tuberculous meningitis; ABM: Acute bacterial meningitis

Hyponatremia was also more common in TBM group but the difference was not significant statistically. Cranial nerve palsy was more common in patients with TBM especially those nerves related to the ocular eye movements. Radiculomyelitis was seen in only one child with ABM but it was more frequent in TBM which was reported elsewhere (8). One patient had syringomyelia during her course of TBM (9). All measured variables revealed significant difference between ABM and TBM patients except for seizure episodes. Multivariate logistic regression analysis shows positive predictive effect of cranial nerve palsy (OR=1.980, CI 95%: 1.161-3.376) and negative predictive effect of neck stiffness (OR=0.476, CI 95%: 0.252-0.899) on the diagnosis of TBM (Table 2).

Table 1. Characteristics of patients with tuberculous and acute bacterial meningitis.

Variables*	ABM (186 patients)	TBM (109 patients)	*P*-value
Age (years) mean ± SD	23.9 ± 18.5	41.1 ± 22.3	<0.001
Disease duration (days) mean ± SD	4.9 ± 5.9	23.2 ± 25.1	<0.001
Male: Female (% male)	133/53 (71.5%)	64/45 (58.7%)	0.017
Seizure disorder	28 (15.1%)	12 (11%)	0.207
Generalized	26	12	
Focal	2	0	
Stroke	37 (20%)	32 (29.9%)	0.039
Cranial nerve palsy	39 (21.1%)	38 (35.5%)	0.006
Loss of consciousness	80 (43%)	56 (51%)	0.059
Neck Stiffness	157 (84.4%)	82 (75.2%)	0.020
Headache (days) mean ± SD	4.6 ± 4.9	20.6 ± 27.3	<0.001
Radiculomyelitis	1 (0.5%)	5 (4.5%)	0.051
Hyponatremia	20 (12.0%)	18 (19.7%)	0.154

*ABM: Acute bacterial meningitis; TBM: Tuberculous meningitis; SD: Standard deviation

Table 2. Lack of significance of seizure, hemiplegia, cranial nerve deficit and decreased level of consciousness as predictive variables to differentiate ABM and TBM.

Variables	Adjusted odds ratio (95% CI)	*P*-value
Cranial nerve palsy	1.980 (1.161-3.376)	0.006
Neck stiffness	0.476 (0.252-0.899)	0.022
Seizure disorder	1.294 (0.623-2.690)	0.272
Stroke	1.207 (0.474-3.070)	0.646
Loss of consciousness	0.624 (0.127-1.269)	0.214

*ABM: Acute bacterial meningitis; TBM: Tuberculous meningitis; CI: Confidence

Discussion

Neurological examination is an important feature of clinical examination for the diagnosis of neuro-infectious disorders. Tuberculous meningitis is usually a progressive disorder and the diagnosis is difficult especially in regions with poor resources. The importance of each finding to differentiate TBM from ABM especially in those areas should be emphasized. In our study cranial nerve palsies with an adjusted odds ratio of 1.98 was the most important neurological predictor factor to differentiate TBM from ABM. Neck stiffness showed a negative chance for diagnosis of TBM with an adjusted odds ratio of 0.47 (Table 2).

Different studies showed that simple clinical and laboratory data can help to differentiate ABM and TBM (10-13). According to our previous study in south-eastern Iran, four features including disease duration more than 5 days before diagnosis, age over 30 years, CSF pleocytosis less than 1000 cells/µl and CSF lymphocytosis more than 70% were independently predictive factors for the diagnosis of TBM (10). Thwaites *et al*. reported that age more than 36 years and history of illness more than 6 days are good predictive factors for discrimination of TBM from ABM (12).

Cranial nerve palsies occurred in 35.5% of our TBM patients and in 20% to 52% of patients in other series (14-16). The number of patients with cranial nerve palsy will be increased from 23% to more than 37% if optic neuropathy and visual impairment included in them (17). Cranial neuropathies, especially oculomotor nerve involvement, and epileptic seizures occurred in 29% and 28% of TBM patients in New Zealand, respectively but the most common complications in long-term survivors in this study were cognitive impairment (12%) and epilepsy (11%) (18). Cranial nerve palsies have been shown as a predictor factor for neurological sequelae with an odds ratio in their of 3.9 (CI 95%: 1.8-8.8) (19). Cranial nerve palsies were reported in 21 and 35% of our patients with ABM and TBM, respectively with an odds ratio of 1.98 (Table 2). However, the stage of the disease when patients admitted to the hospital is an important issue. TBM patients treated in early stages will recover completely five times more than cases admitted later (17). Singhi *et al*. (20) reported that despite the lower incidence of cranial nerve palsy in ABM it has a significant association with neurological sequelae at follow-up. Cranial nerve palsy in their study was seen in 25% of children with ABM excluding cases with hearing loss and blindness but Wu *et al*. had shown the same problem only in two patients out of 24 patients (8%) with *Salmonella* meningitis (21).

Seizures are important neurological complications of bacterial meningitis and occurred in 17% of adults with community-acquired bacterial meningitis and death was observed in 41% of patients with seizures compared to 16% of patients without seizures ($P<0.001$) (22). In another study (23) it was demonstrated that the long-term outcome of adult with ABM and acute seizure episodes produced worse outcomes in comparison to those who had no seizures. There was no difference in the outcome between patients with focal or generalized epileptic phenomena. Mean time for seizure occurrence in ABM group was reported to be 4 days after ABM onset (23). It has been reported that 63% of children with ABM had epileptic attacks, however, only 9% had uncontrolled seizures. Adjusted odds ratio for neurological outcomes and sequelae was 3.99 (CI 95%: 1.26-13.17; $p=0.015$) (20). Vibha *et al.* (24) reported that the presence of seizure was not a predictor of death in the multivariate analysis of different clinical and laboratory factors. Only 5.8% of patients without epileptic episodes died contrary to 17% in the other group. In another study epileptic attacks occurred in 23% of patients with community-acquired meningitis, and 28% had focal central nervous system findings. However, in their study seizure occurrence during the first 24 hours reported to be a risk factor for death in ABM (3). Seizure attacks before

admission and after hospitalization were significantly higher in patients with *Salmonella* meningitis and neurological sequels or death (21). Seizure was demonstrated as a clinical factor in univariate analysis with odds ratio less than one (OR=0.34, CI 95% 0.20-0.50), comparing admission variables between TBM and non-TBM meningitis in Egypt (11) but this significant difference was not shown in our study. The main type of epileptic phenomenon reported in TBM is focal seizure with secondary generalization (17).

Stroke occurs in 45% of patients with TBM both in early or later stage of the disease, and predicts poor outcome at 3 months (25) comparing to 29.9% of stroke in our patients with TBM. It was more prevalent in the territory of lenticulostriate arteries and basal ganglia as it was reported earlier (26). Cerebral infarction can occur in both the acute and chronic stage of TBM (27), it may be silent or symptomatic (28) and the prognosis is poor after cerebral infarction. Focal motor deficit at admission is also reported as an important predictor of neurologic deficits at 1 year (17). The pathophysiologic mechanisms are strangulation, spasm, constriction, periarteritis and even necrotizing panarteritis of vessels due to intensification of basal exudative meningitis of the circle of Willis with or without secondary thrombosis (28). When treating patients with TBM, the possibility of cerebral infarction should be considered especially when patients develop focal neurological signs and meningeal enhancement on a CT scan (29). Stroke in ABM is not as frequent as TBM and sometimes there are hemorrhagic strokes which cause a poor prognosis for the patient (30). Vibha *et al*. (24) reported that 1.7% of their patients with ABM had hemiparesis without any effect on the outcome. However, brain CT scan showed 4.5% of those patients had cerebral infarction at the same time. Another study revealed that eight of 32 patients (25%) had hemiparesis at follow up of survivors of bacterial meningitis but after multivariate regression statistical analysis it could not be shown that stroke is a predictor of sequelae in ABM (20).

Neck stiffness as a major clinical manifestation of ABM reported in 41% of 91 cases (31), however, in another study it was reported that 69% of 41 patients with TBM had neck stiffness (32). Probably chronicity of the disease in TBM group is an important factor resulting in the presence of stiffness and rigidity of cervical muscles. Neck stiffness will decrease after using steroids in the treatment of TBM (33).

There are some limitations in this study. Our center is tertiary care referral center in the region and complicated patients after initial or failed treatment were admitted more and more. Therefore, our patient group is not a true representative of population with tuberculous or bacterial meningitis. The frequency of neurological complications were also underestimated because the study was retrospective, in some earlier patients did not have neuroimaging like, low number of positive CSF cultures and lack of complete data on the incidence and prevalence of disease in many developing countries. The above findings confirm the importance of clinical features, especially neurological ones which play an important role to differentiate between two groups of ABM and TBM patients.

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