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Clinical characteristics of tuberculous meningitis combined with cranial nerve palsy

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ABSTRACT

Objective: To retrospectively analyze the data of 72 patients with tuberculous meningitis (TBM) combined with cranial nerve palsy, to explore the incidence, clinical features, CSF assay changes and outcome in patients with TBM.

Patients and methods: A total of 72 patients were diagnosed as TBM with cranial nerve palsy. The gender, age, clinical manifestations, CSF examinations, cerebral magnetic resonance imaging (MRI) enhancement scan were collected. All these patients had completed at least 2 months of follow up after anti-tuberculous treatment.

Results: This study retrospectively evaluated 486 patients; include 254 (52.3%) men and 232 (47.7%) women. The mean age was 35.2 ± 17.0 years. 72 patients (14.8%) were diagnosed as TBM with cranial nerve palsy. Among them, 38 cases (52.8%) had optic nerve palsy (the 2nd nerve), 41 cases (56.9%) had oculomotor nerve palsy (the 3rd nerve), 3 cases (4.2%) had abducens nerve palsy (the 6th nerve), and 10 cases (13.9%) had auditory nerve palsy (the 8th nerve). 16 patients (22.2%) had two groups of cranial nerve involvement (oculomotor nerve and optic nerve in 10 cases, optic nerve and auditory nerve in 5 cases, and optic nerve and abducens nerve in 1 case). Two patients (2.8%) had three groups of cranial nerve involvement (oculomotor nerve, optic nerve and abducens nerve). CSF MTB was detected by acid fast bacilli (no patient was positive), MTB DNA detection by multiplex polymerase chain reaction (PCR) (3 patients were positive) and MTB cultures (2 patients were positive). There was no significant difference of CSF cells and biochemistry investigations between the patients with or without cranial nerve palsy. Magnetic resonance imaging (MRI) enhancement scan were done in 66 (91.7%) patients after admission. It was abnormal in 57 (86.3%) patients. 15 cases (26.3%) had meningeral enhancement, 25 cases (43.9%) had tuberculoma, 11 cases (19.3%) had hydrocephalus and 6 cases (10.5%) with infarct. All patients were followed up after 2 months of anti-tuberculous treatment. 70 patients (97.2%, 70/72) with the cranial nerve palsy were fully recovered without obvious sequel.

Conclusion: The complications of cranial nerve palsy in TBM patients are not uncommon, and the rate of misdiagnosis is high, which makes them vulnerable to emergencies such as disturbance of consciousness. Effective anti-tuberculous treatment can restore most cranial nerve palsy.

1. Introduction

Tuberculous meningitis (TBM) is one of the most common and the most severe form of extra pulmonary tuberculous disease. Early diagnosis and effective treatment is essential to avoid morbidity and mortality. Because TBM presents with no typical symptoms and signs in the early stage and there is no *M. tuberculous (MTB)* organism in cerebrospinal fluid (CSF), the early diagnosis is quite challenging. The diagnosis is easy to definite when severe nervous system damages occurred, such as coma, epileptic seizures, and elevated intracranial pressure. Delay in diagnosis and treatment is related to extremely poor outcome. Cranial nerve palsy is the most important neurological predictor factor to differentiate TBM from other cause of meningitis [1]. It occurred in more than one third of patients with tuberculous meningitis. Severe cranial nerve injury can cause focal neurologic deficit, such as blindness and deafness and the presence of cranial neuropathy was associated with poor outcome [2]. This study retrospectively evaluated the incidence, clinical features, CSF assay changes and outcome in patients with TBM combined with cranial nerve palsy in our hospital.

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2. Patients and methods

2.1. Patients

This retrospective study was conducted in a tuberculosis specialized hospital in north China from June 2014 to December 2017. All patients enrolled (n = 486) underwent clinical evaluation at baseline. A total of 72 patients (14.8%) were diagnosed as TBM with cranial nerve palsy and the other 414 patients (85.2%) were diagnosed as TBM without cranial nerve palsy. The gender, age, clinical manifestations were collected. The CSF was examined for cells, protein, adenosine deaminase (ADA), acid fast bacilli, MTB DNA by multiplex polymerase chain reaction (PCR) and MTB cultures. Cerebral magnetic resonance imaging (MRI) enhancement scan were done to determine the injury of the brain. The location, severity and outcome of cranial nerve palsy were also assessment carefully. All these patients had completed at least 2 months of follow up after anti-tuberculosis treatment.

2.2. Diagnostic criteria

(1) Diagnostic criteria for TBM: According to the clinical criteria, cerebrospinal fluid standards, brain imaging standards, other parts evidence of TB, TBM is divided into confirmed TBM, probable TBM, and possible TBM. *Definite TBM* was diagnosed as *M. tuberculous* detected from the brain or spinal cord on autopsy or CSF, used acid-fast bacill, culture or commercial nucleic acid amplification test; *Probable TBM* was diagnosed as a total diagnostic score of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available); *Possible TBM* was diagnosed as a total diagnostic score of 6–9 points (when cerebral imaging is not available) or 6–11 points (when cerebral imaging is available) [3].
(2) Diagnostic criteria for cranial nerve palsy: Referring to the sixth edition of Neurology published by the People's Medical Publishing House. The damage to the optic nerve or auditory nerve caused by adverse reactions of anti-tuberculous drugs during anti-tuberculous treatment is not included.
(3) TBM grading standards: According to the British Medical Research Council's grading standards [4], TBM is classified into three levels according to its severity. Grade I was defined as awake and had no focal neurological deficits; grade II was a Glasgow Coma Scale (GCS) of 11–14 or 15 but with focal neurological deficits; grade III was GCS ≤ 10 Points, with or without focal neurological deficits.

2.3. Statistical method

The statistical analysis was performed with SPSS 17.0 software (Chicago, IL, USA). Data of normal distribution were expressed as *mean ± Standard Deviation (SD)*, and two independent sample *t*-tests were used for comparison; Data that did not meet the normal distribution were expressed by medians (quartiles), two independent sample *U* test were used for comparison; $\chi 2$ or Fisher's exact test were used to compare the rate of the two groups. The statistically significant was defined at $P < 0.05$.

3. Results

3.1. Demographic data and clinical features

This study retrospectively evaluated 486 patients with TBM who were admitted in the hospital from June 2014 to December 2017; include 254 (52.3%) men and 232 (47.7%) women. The mean age was 35.2 ± 17.0 years (range 8–85 years). Out of whom, 72 patients were diagnosed as TBM with cranial nerve palsy and the other 414 patients were diagnosed as TBM without cranial nerve palsy. Among them, 5 patients were diagnosed as confirmed TBM (2 were based to CSF culture, 3 were based to PCR). 51 patients were probable TBM and 17 patients were possible TBM. The patients were divided into three stages according to the severity: 36 cases were classified as stage I (17 males, 19 females, mean age 37.6 ± 15.8 years). 17 cases were stage II (5 males, 12 females, mean age 33.3 ± 17.1 years). 19 cases were stage III (9 males, 10 females, mean age 30.4 ± 17.8 years) (Table 1).

Table 1
Demographic data and clinical features.

	TBM with cranial nerve palsy(n = 72)	TBM without cranial nerve palsy(n = 414)	P value
Age(years)	34.8 ± 16.7	35.3 ± 17.1	0.817
Sex			0.106
male	31(43.1)	221(53.4)	
female	41(56.9)	193(46.6)	
Duration of disease (days)	30 (20,60)	30(15,60)	0.828
Primary/Retreatment (case)	57/15	325/89	0.899
Diagnosis			
Definite TBM	5(7.0)	16(3.9)	0.236
Probable TBM	50(69.4)	209(50.5)	0.003
Possible TBM	17(23.6)	189(45.7)	0.000
Staging			
I	36(50)	198(47.8)	0.733
II	17(23.6)	116(20.8)	0.439
III	19(26.4)	100(24.2)	0.684
Major occupation			
Agricultural labor (%)	21(29.2)	142(34.3)	0.395
Unemployed (%)	10(13.9)	69(16.7)	0.555
Student (%)	11(15.3)	73(17.6)	0.626
Symptoms			
Fever (%)	65(90.3)	320(77.3)	0.012
Headache (%)	65(90.3)	276(66.7)	0.000
Nausea and vomit (%)	41(56.9)	94(22.7)	0.000
Unconscious	39(54.2)	130(31.4)	0.000
Misdiagnosis rate (%)	28(38.9)	107(25.8)	0.023
Mortality (%)	1(1.4)	10(2.4)	0.589
Perinatal period	6(8.3)	12(2.9)	0.024
intracranial pressure	205.0 ± 91.9	206.8 ± 89.0	0.892

There was no significant difference of age, male ratio, proportion of primary/retreatment patients, staging of severity and major occupations in TBM patients with cranial nerve palsy compared with the patients without palsy. There was no significant difference between the length duration of TBM in presence or absence of cranial nerve palsy patients (30 (20, 60) days vs 30(15, 60) days, $P = 0.828$). There was also no significant difference between the intracranial pressure of TBM in presence and absence of cranial nerve palsy patients (205.0 ± 91.9 cmH_2O vs 206.8 ± 89.0 cmH_2O, P = 0.892) (Table 1).

The most common symptom is fever (88.9%, 64/72). TBM patients with cranial nerve palsy had more fever (90.3% vs 77.3%, $\chi^2 = 6.280$, $P = 0.012$), headache (90.3% vs 66.7%, $\chi^2 = 16.334$, $P = 0.000$), nausea and vomiting (56.9% vs 22.7%, $\chi^2 = 35.840$, $P = 0.000$) and unconscious (54.2% vs 31.4%, $\chi^2 = 14.015$, $P = 0.000$) than non- palsy patients. There were 6 patients in the perinatal period with cranial nerve palsy, which was more than patients without cranial nerve palsy ($\chi^2 = 5.079$, $P = 0.024$) (Table 1).

3.2. Features of cranial nerve palsy

Among the 72 patients, 38 cases (52.8%) had optic nerve palsy (the 2nd nerve), 41 cases (56.9%) had oculomotor nerve palsy (the 3rd nerve), 3 cases (4.2%) had abducens nerve palsy (the 6th nerve), and 10 cases (13.9%) had auditory nerve palsy (the 8th nerve). Among them, 16 patients (22.2%) had two groups of cranial nerve involvement (oculomotor nerve and optic nerve in 10 cases, optic nerve and auditory nerve in 5 cases, and optic nerve and abducens nerve in 1 case). Two

Table 2
Various patterns of cranial nerve palsy in patients with TBM.

cranial nerve involvement	Number of patients
2nd nerve	38
3rd nerve	41
6th nerve	3
8th nerve	10
2nd and 3rd nerve	10
2nd and 8th nerve	5
2nd and 6th nerve	1
2nd, 3rd and 6th nerve	2

patients (2.8%) had three groups of cranial nerve involvement (oculomotor nerve, optic nerve and abducens nerve) (Table 2).

3.3. Misdiagnosis

28 patients were misdiagnosed before admission and the misdiagnosis rate was 38.9% (28/72). The main misdiagnosis diseases were upper respiratory tract or lung infection (53.6%, 15/28), meningitis due to other causes (14.3%, 4/28), cerebrovascular disease (14.3%, 4/28), and gastrointestinal disorders (7.1%, 2/28), and one case was misdiagnosed as early pregnancy reaction, anemia, and cervical spondylosis, respectively.

3.4. Evidence of TB elsewhere

Evidence of TB elsewhere in the body was found in 68 (94.4%, 68/72) patients with cranial nerve palsy. 59(86.8%, 59/68) of them had pulmonary/Pleural tuberculous and 17(25.0%, 17/68) of them had extra pulmonary tuberculosis (Table 3). Five (7.4%, 5/68) patients were combined with more than two sites of extra pulmonary tuberculosis.

3.5. CSF and MRI examination

CSF analysis was performed in all patients. MTB was detected by acid fast bacilli (no patient was positive), MTB DNA detection by multiplex polymerase chain reaction (PCR) (3 patients were positive) and MTB cultures (2 patients were positive). There was no significant difference of CSF cells and biochemistry investigations between the patients with or without cranial nerve palsy (Table 4).

Magnetic resonance imaging (MRI) enhancement scan were done in 66 (91.7%) patients after admission. It was abnormal in 57 (86.3%) patients. 15 cases (26.3%) had meningeral enhancement, 25 cases (43.9%) had tuberculoma, 11 cases (19.3%) had hydrocephalus and 6 cases (10.5%) with infarct (Table 4).

3.6. Prognosis

All patients were followed up after 2 months of anti-tuberculous treatment. 70 patients (97.2%, 70/72) with the cranial nerve palsy was fully recovered without obvious sequel. Only 2 patients (2.8%, 2/72) left sequel, which were oculomotor and optic nerve palsy, respectively.

Table 3
Evidence of TB elsewhere.

	Number of cases	Percentage (%)
Pulmonary/Pleutral tuberculous	59	86.8
Extrapulmonary tuberculous	17	25.0
Lymph node tuberculous	7	41.2
Bone tuberculous	9	52.9
Knee tuberculous	3	17.6
Abdomen tuberculous	4	23.5

Table 4
Comparison of CSF and MRI parameters in TBM patients with and without cranial nerve palsy.

	TBM with cranial nerve palsy(n = 72)	TBM without cranial nerve palsy(n = 414)	*P* value
MRI abnormalities			
Meningeal enhencement	22(38.6)	100(31.4)	0.287
Tuberculoma	36(63.2)	245(77.0)	0.031
Hydrocephalus	11(19.3)	68(21.4)	0.860
Infarct	6(10.5)	41(12.9)	0.828
CSF leukocytes ($\times 10^3$/Ul)	60(18,150)	52(12,145)	0.550
CSF ADA (U/L)	5.0(2.2,8.8)	5.2(2.1,8.3)	0.888
CSF sugar (mmol/L)	2.1(1.4,2.7)	2.3(1.6,3.0)	0.061
CSF chloride (mmol/L)	114.4(109.9,121.5)	116.3(110.5,121.1)	0.503
CSF protein (g/L)	105.7(71.2,156.9)	97.8(56.8,162.4)	0.290

4. Discussion

Tuberculous meningitis was the most serious form of tuberculosis, the mortality rate is 26.8% [5], and 20%–30% of surviving patients had persistent sequel of the central nervous system [6]. Sharma et al. [7] reported that the incidence of TBM with cranial nerve palsy was 38%, abducens nerve was the most commonly affected cranial nerve (32.3%), and 10% of patients had two or more groups of cranial nerve involvement. This study showed that the incidence of TBM with cranial nerve palsy was 14.8%, of which the oculomotor nerve (56.9%) was the most affected cranial nerve, followed by optic nerve (52.8%), auditory nerve (13.9%) and abducens nerve (4.2%), 26.3% of patients had two or more groups of cranial nerve involvement. However, cranial nerve palsy is not uncommon in patients with TBM. Cerebral MRI enhancement scan can found corresponding cranial neuritis performance, which has important value in the observation of efficacy and evaluation of prognosis. There was significant positive association between presence of hydrocephalus (p = 0.05; OR = 2.2; 95% CI = 0.97–5.1) with either death or survival with severe disability [8].Therefore, MRI scan should be routinely performed for suspected TBM patients.

The pathological processes of TBM include: (1) obstruction of CSF caused by inflammatory exudates leading to hydrocephalus; (2) granulomatous lesions that form tuberculoma or abscess, leading to focal neurological deficits; (3) occlusive vasculitis leading to infarction and stroke. Studies have shown that cranial nerve palsy is closely related to the degree of intracranial lesions, and has a positive predictive effect on the diagnosis of TBM (AOR = 1.980, CI 95%: 1.161–3.376), which is the most important nerve predictors for distinguishing TBM from bacterial meningitis [1]. The incidence of cranial nerve palsy was higher in grade III (75%) than in grade II (43%) and grade I (24%) patients [9]. Therefore, patients with cranial nerve palsy appear on admission, and their neurological sequelae are more common [10]. This study also showed that the incidence of disturbance of consciousness in TBM patients with cranial nerve palsy was significantly higher than those without cranial nerve palsy (54.2% vs 31.4%, $P = 0.000$), and cranial nerve palsy was significantly associated with the occurrence of disturbance of consciousness.

This study showed that the misdiagnosis rate of TBM patients with cranial nerve palsy was significantly higher than those without cranial nerve palsy (38.9% vs. 25.8%, $P = 0.023$). The main misdiagnosis diseases included upper respiratory tract or lung infection (53.6%, 15/28), meningitis due to other causes (14.3%, 4/28), cerebrovascular disease (14.3%, 4/28), and gastrointestinal diseases (7.1%, 2/28). This may be related to the atypical clinical symptoms and signs of the disease. If the patient cannot be diagnosed with TBM in time, the more severe the cranial nerve palsy is, the more likely concomitant with the disturbance of consciousness which will affect the patient's prognosis.

Therefore, rapid and accurate diagnosis and early treatment are important factors to improve the prognosis of TBM patients. However, the diagnosis of TBM currently lacks diagnostic methods with high sensitivity and specificity. The positive rate of bacteriological examination in cerebrospinal fluid is low, and the imaging examination is lacking in specificity. Immunology is not a direct evidence of tuberculous infection, and it is impossible to distinguish between active diseases or latent infection. The most common symptom of cranial nerve palsy with TBM was fever (90.3%, 65/72). Therefore, patients with cranial nerve palsy associated with fever should consider the possibility of TBM, and timely conduct relevant examinations to confirm the diagnosis.

TBM combined cranial nerve palsy can be restored after anti-tuberculous treatment. In this group of 70 patients, cranial nerve damage has almost recovered at 2 months follow-up, and only 2 patients left oculomotor nerve and optic nerve palsy. It suggests that the cranial nerve palsy is a reversible change; timely and effective anti-tuberculous treatment can reduce the occurrence of palsy and reduce the damage caused by the palsy.

In summary, complications of cranial nerve palsy in TBM patients are not uncommon, and the rate of misdiagnosis is high. If the patient cannot be diagnosed and treated in timely, they are susceptible to emergencies such as disturbance of consciousness. Effective anti-tuberculous treatment can restore most cranial nerve injuries. Therefore, exploring more sensitive and rapid detection method is very important for the diagnosis of TBM. Clinicians should also carefully look for clues of TBM and cranial nerve palsy to reduce the occurrence of squeal.

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No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

References

[1] A. Moghtaderi, R. Alavi-Naini, S. Rashki, Cranial nerve palsy as a factor to differentiate tuberculous meningitis from acute bacterial meningitis, Acta Med. Iran. 51 (2) (2013) 113–118 16.

[2] M.K. Sinha, R.K. Garg, Hk Anuradha, et al., Vision impairment in tuberculous meningitis: predictors and prognosis, J. Neurol. Sci. 290 (1–2) (2010) 27–32, https://doi.org/10.1016/j.jns.2009.12.012 15.

[3] S. Marais, G. Thwaites, J.F. Schoeman, et al., Tuberculous meningitis: a uniform case definition for use in clinical research, Lancet Infect. Dis. 10 (11) (2010) 803–812, https://doi.org/10.1016/S1473-3099(10)70138-9.

[4] G.E. Thwaites, D.B. Nguyen, H.D. Nguyen, et al., Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults, N. Engl. J. Med. 351 (2004) 1741–1751, https://doi.org/10.1056/NEJMoa040573.

[5] S. Jullien, H. Ryan, M. Modi, et al., Six months therapy for tuberculous meningitis, Cochrane Database Syst. Rev. 9 (2016) CD012091, , https://doi.org/10.1002/14651858.CD012091.pub2.

[6] A.A. Joosten, P.D. van der Valk, J.A. Geelen, et al., Tuberculous meningitis: pitfalls in diagnosis, Acta Neurol. Scand. 102 (2000) 388–394 https://doi.org/10.1034/j.1600-0404.2000.102006388.x.

[7] P. Sharma, R.K. Garg, R. Verma, et al., Incidence, predictors and prognostic value of cranial nerve involvement in patients with tuberculous meningitis: a retrospective evaluation, Eur. J. Intern. Med. 22 (June (3)) (2011) 289–295, https://doi.org/10.1016/j.ejim.2011.01.007.

[8] M. Modi, K. Sharma, S. Prabhakar, et al., Clinical and radiological predictors of outcome in tubercular meningitis: a prospective study of 209 patients, Clin. Neurol. Neurosurg. 161 (October) (2017) 29–34, https://doi.org/10.1016/j.clineuro.2017.08.006.

[9] K. Sher, Firdaus, A. Abbasi, et al., Stages of tuberculous meningitis: a clinicoradiologic analysis, J. Coll. Phys. Surg. 23 (6) (2013) 405–408 doi: 06.2013/JCPSP.405408.

[10] F. Pehlivanoglu, K.K. Yasar, G. Sengoz, Prognostic factors of neurological sequel in adult patients with tuberculous meningitis, Neurosciences (Riyadh) 15 (4) (2010) 262–267.