


Incidence and Risk Factors of Cranial Nerve Palsy in Patients with Tuberculous Meningitis: A Retrospective Evaluation

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Objective: Tuberculous meningitis (TBM) is a common form of central nervous system (CNS) tuberculosis (TB). Cranial nerve palsy is a serious complication of TBM. Literature regarding this subject is still limited in China. This study evaluated the incidence of cranial nerve palsy in patients with TBM in South China, its association with the clinical forms of TB, and other patient characteristics.

Methods: A retrospective chart review of patients with a diagnosis of TBM between January 2004 and December 2019 was conducted, and the demographic characteristics, clinical characteristics, and laboratory results of 114 patients were collected and followed up for 3 months. A multivariate logistic regression analysis model was used to explore the risk factors of cranial nerve palsy in patients with TBM.

Results: A total of 114 patients were enrolled in this study. Cranial nerve palsy was observed in approximately 38 (33.3%) of TBM patients. Among them, 13 (28.3%) had optic nerve palsy, 24 (52.2%) had oculomotor nerve palsy, 5 (10.9%) had abducens nerve palsy, 2 (4.3%) had auditory nerve palsy, 1 (2.2%) had glossopharyngeal nerve palsy, and 1 (2.2%) had vagus nerve palsy. Using logistic regression analysis, focal neurological deficit, extracranial TB and cerebrospinal fluid (CSF) total white cell count (WCC) were shown to be risk factors for cranial nerve palsy.

Conclusion: The prevalence rate of cranial nerve palsy was 33.3% in patients with TBM. Focal neurological deficits, extracranial TB and CSF total WCC are important predictors of cranial nerve palsy in patients with TBM.

Keywords: tuberculous meningitis, tuberculosis, cranial nerve palsy, risk factors, prediction

Introduction

In 2019, an estimated 10 million people developed tuberculosis (TB) and 1.4 million died, according to the World Health Organization (WHO) Global Tuberculosis Report 2020.¹ Today, TB remains the most common cause of death from a single source of infection worldwide. China is a country with a high TB burden, with approximately 833,000 new cases in 2019, accounting for 8.4% of new TB cases.^{1,2} Tuberculous meningitis (TBM) is a serious and critical presentation of extrapulmonary TB caused by *Mycobacterium tuberculosis* (MTB) infection, with high rates of mortality and disability,^{3,4} especially among children and people living with HIV in developing countries.^{5,6}

Cranial nerve palsy is a common complication of TBM. Recent studies have found that people with TBM are more likely to develop cranial nerve palsy than those with other central nervous system (CNS) infections and healthy controls.⁷⁻⁹ Unfortunately, a study has shown that cranial nerve palsy is associated with high mortality and disability in TBM.¹⁰ However, no study has assessed the incidence of cranial nerve palsy in patients with TBM and its associated factors in China. This study described the prevalence of cranial nerve palsy and its associated risk factors in patients with TBM in southern China.

Methods and Materials

Patient Recruitment

A retrospective study was conducted from January 2004 to December 2019 at the Neurology ward of Jiangxi Provincial People's Hospital and Infectious Diseases Hospital of Jiangxi Province, serving approximately 45.2 million people in South China. Consecutive patients (aged ≥ 16 years) with a suspected diagnosis of TBM were enrolled. Patients with incomplete case data, unclear diagnoses, other intracranial infections, and HIV seropositivity were excluded. All patients received four standard anti-tuberculosis treatment regimen for the first 2 ~ 3 months, including isoniazid (300 ~ 600 mg per day), rifampicin {450 mg per day (weight < 50kg) or 600 mg per day (weight ≥ 50 kg)}, pyrazinamide (25 mg/kg per day), and ethambutol (15 mg/kg per day), and were followed up for at least 3 months.

Definitions

Diagnostic Criteria for TBM

TBM was divided into “definite”, “probable”, and “possible”, based on the case definitions proposed by Marais et al who described a diagnostic scoring system including the clinical criteria, cerebrospinal fluid (CSF) standards, radiologic criteria, and other evidence of TB outside the CNS (see Table 1).¹¹ Definite TBM was diagnosed by smear microscopy for acid-fast bacteria (AFB) in CSF or culture or positive polymerase chain reaction for the MTB test. Probable TBM was diagnosed if a total score of 12 or more points (when cerebral imaging was not available, the total score decreased to

Table 1 The Marais Criteria for the Diagnosis of TBM on Admission

	Diagnostic Score
Clinical Criteria	(Maximum Category Score = 6)
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children <10 years of age)	2
Focal neurological deficit (excluding cranial palsies)	1
Cranial nerve palsy	1
Altered consciousness	1
CSF Criteria	(Maximum Category Score = 4)
Clear appearance	1
Cells: 10–500 per μ L	1
Lymphocytic predominance (>50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2.2 mmol/L	1
Cerebral Imaging Criteria	(Maximum Category Score = 6)
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Pre-contrast basal hyperdensity	2
Evidence of Tuberculosis Elsewhere	(Maximum Category Score = 4)
Chest radiograph suggestive of active tuberculosis signs of tuberculosis = 2; miliary tuberculosis = 4	2/4
CT/MRI/Ultrasound evidence for tuberculosis outside the CNS	2
AFB identified or <i>Mycobacterium tuberculosis</i> cultured from another source-ie, sputum, lymph node, gastric washing, urine, blood culture	4
Positive commercial <i>M. tuberculosis</i> NAAT from extra-neural specimen	4
Exclusion of alternative diagnoses	

Abbreviations: TST, Tuberculin skin test; IGRA, Interferon-gamma release assay; NAAT, Nucleic acid amplification test; AFB, Acid-fast bacilli.

10 or more points), while it was compatible between patients who received a score of 6–11, and who were possible TBM (when cerebral imaging was unavailable, the score of 6–9 points).

TBM Grading Standards

The severity of TBM at admission was assessed according to British Medical Research Council (BMRC) criteria based on the patients' Glasgow Coma Score (GCS) and focal neurological deficits.¹² Stage I was defined as a GCS of 15 points without focal neurological deficits; stage II was defined as a GCS of 15 points with neurological deficits or a GCS of 11–14 points; stage III was defined as a GCS of ≤ 10 points. The diagnostic criteria for cranial nerve palsy referred to the eighth edition of Neurology published by the Chinese People's Medical Publishing House.^{9,13} Patients with abnormal fundus exam without obvious visual impairment were excluded.

Procedures

All patients enrolled were subjected to a detailed history-taking and physical examination at baseline. Clinical case data of all patients were collected. The following information (clinical signs and symptoms) was recorded: body temperature, night sweats, headache, nausea and vomiting, seizures, weight loss history, altered consciousness, duration of illness, psychiatric symptoms, focal neurological deficits (combination of slurred speech, crooked corners of the mouth, numbness, and weakness), extracranial TB, GCS score, TBM score, anorexia, and TBM severity grades. Routine laboratory tests, including blood white cell count (WCC), blood neutrophils percentage, blood lymphocytes percentage, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum sodium, serum chloride, anti-TB antibody (TB-Ab), hemoglobin (HB), and T-cell enzyme-linked immuno-spot assay (T-spot) were performed. All patients underwent lumbar puncture to obtain CSF samples, and the following tests were performed: total cell count and chloride, glucose, and protein levels. CSF samples were centrifuged, and the sediments were stained (mycobacterial smears) and cultured (common bacterial and fungal culture for all patients, Lowenstein–Jensen media for 6). To be enrolled, chest X-rays and cranial CT/MRI scans were obtained in all patients at admission.

Statistical Analysis

Statistical calculations were performed using SPSS version 17.0. The 40 clinical and laboratory parameters of patients with and without cranial nerve palsy are compared in Table 2. Data are expressed as mean \pm standard deviation (SD) in cases of normal distribution, and median (interquartile range) in cases of non-normal distribution. The *t*-test or Mann–Whitney *U*-test was used to compare the two groups of continuous variables and categorical variables were expressed as numbers and percentages, and analyzed using the χ^2 -test or Fisher's exact test. A *p*-value of < 0.05 was considered statistically significant. The odds ratios and 95% confidence intervals were calculated. Logistic regression analysis with a stepwise forward variable selection procedure was performed to investigate the independent effects of the determined significant variables between the groups.

Results

Demographic Data and Clinical Features of the Enrolled Participants

During the study period, 134 patients with TBM were entered into the study; however, 20 (15%) patients were excluded as their diagnoses uncertain or their data were incomplete. Among the 114 patients we studied, 69 (60.5%) were men and 45 (39.5%) were women. Only 12 (10.5%) patients had a definitive diagnosis (all were based on CSF smear, no patient was MTB culture-positive), 79 (69.3%) had a probable diagnosis, and 23 (20.2%) had a possible diagnosis based on the Marais score criteria.¹¹ All patients received anti-TB treatment after admission, and none had taken anti-TB drugs before admission. Fifty-nine (74.6%) patients had extracranial TB in hospitalization (see Table 3, Figure 1).

Among TBM patients, blood tests revealed anemia (Hb: men < 120 g/L, female < 110 g/L) in 33 (28.9%) patients. The WCC ranged from 10–500 mm³/mL in 27 (23.6%) patients, and neutrophilic granulocyte percentage was $\geq 70\%$ in 82 (71.9%). No patients had an HIV infection. CSF analysis was performed in all patients: the CSF smear for AFB was positive in 12 (10.5%) patients, but none of the CSF culture tests were positive. On CSF examination, the median

Table 2 Univariate Analysis, Comparison of the Clinical and Laboratory Characteristics in Tuberculous Meningitis with and without Cranial Nerve Palsy

Variables	Cranial Nerve Palsy (n=38)	Without Cranial Nerve Palsy (n=76)	Univariate Analysis		
	N (%); $\bar{X}\pm S$; M \pm IR	N (%); $\bar{X}\pm S$; M \pm IR	OR (95% CI)	Statistics	P-value
Clinical features					
Body temperature ^a	37.25 \pm 0.94	37.25 \pm 0.74		t=0.461	0.646
Age (y) ^b	45.13 \pm 18.93	40.86 \pm 17.22		t=-1.209	0.229
Male: Female (Male %) ^c	22:16(57.8%)	47:29(61.8%)	0.85(0.38–1.88)	X ² =0.165	0.684
Night sweats (%) ^c	12(31.6%)	9(11.8%)	3.44(1.30–9.12)	X ² =6.567	0.010
Headache (%) ^c	30(78.9%)	70(92.1%)	0.32(0.10–1.00)	X ² =2.942	0.086
Nausea and Vomiting (%) ^c	15(39.5%)	28(36.8%)	1.12(0.50–2.49)	X ² =0.075	0.785
Seizures (%) ^c	5(13.2%)	5(6.6%)	2.15(0.58–7.95)	X ² =0.671	0.413
Stiff-neck (%) ^c	28(73.7%)	45(59.2%)	1.93(0.82–4.53)	X ² =2.304	0.129
Weight loss history (>10%)(%) ^c	14(36.8%)	22(28.9%)	1.44(0.63–3.30)	X ² =0.740	0.390
Altered Consciousness (%) ^c	21(55.3%)	23(30.3%)	2.85(1.27–6.37)	X ² =6.681	0.010
Duration of illness (d) ^b	63.29 \pm 128.58	31.54 \pm 44.79		t=-1.704	0.088
TBM diagnosis^c					
Definite TBM	8(21.1%)	4(5.3%)	4.80(1.34–17.15)	X ² =5.134	0.023
Probable TBM	20(52.6%)	59(77.6%)	0.32(0.14–0.74)	X ² =7.442	0.006
Possible TBM	10(26.3%)	13(17.1%)	1.73(0.68–4.47)	X ² =1.334	0.248
Psychiatric symptoms (%) ^c	8(21.1%)	13(17.1%)	1.29(0.48–3.45)	X ² =0.263	0.608
Focal neurological deficit (%) ^{8,c}	25(65.8%)	16(21.1%)	7.21(3.02–17.18)	X ² =22.015	0.000
Extracranial TB (%) ^c	23(60.5%)	36(47.4%)	1.70(0.77–3.76)	X ² =1.757	0.185
GCS score ^b	15 \pm 5	15 \pm 2		Z=-0.824	0.410
TBM score ^{a,*}	12.55 \pm 2.30	11.74 \pm 2.90		t=983	0.330
Anorexia (%) ^c	20(52.6%)	42(55.3%)	0.95(0.43–2.10)	X ² =0.015	0.090
BMRC grades^{c,#}					
I (%)	8(21.1%)	47(61.8%)	0.17(0.07–0.41)	X ² =16.88	0.000
II (%)	12(31.5%)	25(32.9%)	0.94(0.41–2.17)	X ² =0.020	0.888
III (%)	18(47.4%)	4(5.3%)	16.20(4.92–53.32)	X ² =28.838	0.000
Blood tests					
Blood WCC ($\times 10^9/L$) ^b	7.75 \pm 3.9	7.5 \pm 3.9		Z=-0.837	0.403
Blood % neutrophils (%) ^b	0.78 \pm 0.17	0.78 \pm 0.12		Z=-0.106	0.915
Blood % lymphocytes (%) ^a	0.16 \pm 0.11	0.15 \pm 0.10		t=-0.155	0.877
Serum sodium (mmo l/L) ^a	131.59 \pm 9.05	134.23 \pm 6.38		t=1.569	0.122
Serum chloride (mmo l/L) ^a	95 \pm 8.03	96.40 \pm 5.77		t=1.001	0.319
Erythrocyte sedimentation rate (mm/h) ^b	21 \pm 33	16.5 \pm 19		Z=-1.39	0.164
C-reaction protein (mg/L) ^b	10.20 \pm 33.05	3.91 \pm 11.51		Z=-2.011	0.044
CSF tests					
Clear CSF appearance (%) ^c	28(73.7%)	56(73.7%)	1.0(0.41–2.42)	X ² =0.000	1.000
CSF total WCC ($\times 10^6/mL$) ^b	270 \pm 448	140 \pm 250		Z=-2.276	0.023
CSF neutrophils ($\times 10^6/mL$) ^b	101 \pm 232	26 \pm 142		Z=-0.488	0.625
CSF % neutrophils (%) ^b	0.3 \pm 0.29	0.25 \pm 0.55		Z=-0.534	0.593
CSF lymphocytes ($\times 10^6/mL$) ^b	85 \pm 345	95.5 \pm 100		Z=-0.379	0.705
CSF % lymphocytes (%) ^b	0.54 \pm 0.31	0.59 \pm 0.28		t=0.887	0.378
CSF/blood glucose ratio ^b	0.37 \pm 0.23	0.36 \pm 0.18		t=-0.262	0.794
CSF chloride (mmo l/L) ^b	115 \pm 11	114 \pm 10		Z=-0.527	0.598
CSF protein (mg/dL) ^b	133.6 \pm 59.5	138.3 \pm 91		Z=-1.061	0.289
CSF opening pressure (mmH ₂ O) ^b	200 \pm 130	200 \pm 133		Z=-0.443	0.658

Notes: ⁸Focal neurological deficit (excluding cranial palsies). The variables were investigated using visual (plots/histograms) and analytical methods (Kolmogorov-Smirnov test) to determine whether these are normally distributed. As the variables are normally distributed, data were expressed as the "Mean \pm Standard deviation ($\bar{X}\pm S$)", if the variables did not show normal distribution ($p < 0.05$), data were expressed as the "median \pm interquartile ranges (M \pm IR)" for continuous variables; The Independent Samples T-Test or Mann-Whitney U-test was used to compare continuous variables between the two groups. And frequency (%) for categorical variables, the qualitative data was analyzed by using ^cchi-square or ^dFisher's exact test.

Abbreviations: OR, Odds ratio; CI, Credibility interval; TBM score^{*}, Thwaites' diagnostic scoring; BMRC grades[#], The modified British Research Council clinical criteria for TM severity grades; ESR, E sedimentation rate (Reference range: Male 0–15mm/h, Female 0–20mm/h); CRP, C-reaction protein (Reference range: 0–8mg/L); CSF, Cerebrospinal Fluid; WCC, White-cell count.

Table 3 Sociodemographic and Clinical Characteristics in Patients with TBM from 2004 to 2019 (N=114)

Characteristics	Total Patients (n=114)	Cranial Nerve Palsy (n=38)	Without Cranial Nerve Palsy (n=76)
	N; $\bar{X}\pm S$; M \pm IR	N; $\bar{X}\pm S$; M \pm IR	N; $\bar{X}\pm S$; M \pm IR
Sociodemographic characteristics			
Male:Female	69:45	22:16	47:29
Age (y) [#]	44.50 \pm 29.25	45.13 \pm 18.93	40.86 \pm 17.22
Weight loss history (>10%)	36	14	22
Known BCG vaccination	101/108	31/36	70/72
Tuberculous symptoms*	85	30	55
Known TB contact history	59/90	22/30	37/60
Cough \geq 2 weeks	26	9	17
HIV co-infection	2/102	2/35	0/76
Body temperature [‡]	37.30 \pm 0.87	37.25 \pm 0.94	37.25 \pm 0.74
Duration of illness before admission (d) [#]	20 \pm 23.5	63.29 \pm 128.58	31.54 \pm 44.79
Clinical characteristics			
Headache (%)	100	30	70
Seizures (%)	10	5	5
Altered Consciousness (%)	40	21	23
Psychiatric symptoms (%)	21	8	13
Focal neurological deficits (%) ^{&}	41	25	16
TBM diagnosis			
Definite TBM	12	8	4
Probable TBM	79	20	59
Possible TBM	23	10	13
GCS score [#]	15 \pm 2	15 \pm 5	15 \pm 2
TBM MRC grades			
I (%)	55	8	47
II (%)	37	12	25
III (%)	22	18	4

Notes: [#]The variables did not show normal distribution, data were expressed as the “median \pm interquartile ranges (M \pm IR)” for continuous variables. [‡]The variables are normally distributed, data were expressed as the “Mean \pm Standard deviation ($\bar{X}\pm S$)” for continuous variables. *Include night sweats, fatigue, loss of appetite, afternoon low fever, and emaciation: three out of five indicators were met. [&]Focal neurological deficit (excluding cranial palsies).

opening pressure of CSF was 17 cmH₂O (9–40), and the intracranial pressure increased (\geq 25 cmH₂O) in 71 (62.3%) patients (see Table 4).

Electroencephalogram testing was performed in all adults and was abnormal in 53 (75.5%) patients. All patients also underwent chest radiographs and cranial CT or MRI scans after admission, wherein signs suggestive of active pulmonary TB were observed in 52 (46%) cases, tuberculoma in 12 (10.6%), hydrocephalus in 36 (31.9%), cerebral infarction in 57 (50.4%), and meningeal reinforcement in 74 (66.1%) (see Figure 2).

Prevalence and Features of Cranial Nerve Palsy

Cranial nerve palsy occurred in 33.3% of the 114 patients with TBM in the present study. Among them, there were 13 (28.3%) cases of optic nerve palsy (the 2nd nerve), 24 (52.2%) cases of oculomotor nerve palsy (the 3rd nerve), 5 (10.9%) cases of abducens nerve palsy (the 6th nerve), 2 (4.3%) cases of auditory nerve palsy (the 8th nerve), 1 (2.2%) case of glossopharyngeal nerve palsy (the 9th nerve), and 1 (2.2%) case of vagus nerve palsy (the 10th nerve). In the cranial nerve palsy group, six (13.0%) patients had two groups of cranial nerve palsy (optic nerve palsy and oculomotor nerve palsy in two cases, optic nerve palsy and abducens nerve palsy in one case, oculomotor nerve palsy and abducens nerve palsy in two cases, and glossopharyngeal nerve palsy and vagus nerve palsy in one case). One (2.2%) patient had three groups of cranial nerve palsy (optic nerve palsy, oculomotor nerve palsy, and auditory nerve palsy). There were no significant differences in sex or age between the cranial nerve palsy and non-cranial nerve palsy groups ($P > 0.05$) (see Table 5).

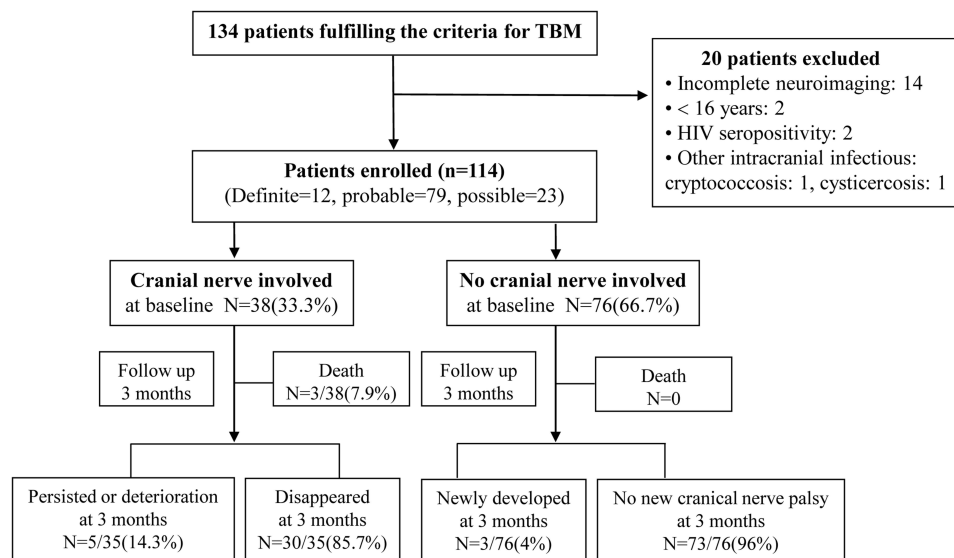


Figure 1 Flow chart of the study.

At enrollment, among the 38 patients with cranial nerve palsy, the main symptoms were headache in 30 (78.9%) patients, nausea and vomiting in 15 (39.5%), and weight loss in 14 (36.8%). The most common clinical signs were: stiff-neck in 28 (73.7%) patients, focal neurological deficit in 25 (65.8%), and altered consciousness in 21 (55.3%). During hospital admission, according to the modified BMRC criteria for TBM severity, 8 (21.1%) cases were TBM grade I, 12 (31.5%) were TBM grade II, and 18 (47.4%) were TBM grade III.

Evidence of Extracranial TB Infection

Twenty-three (60.5%) patients had extracranial TB in the cranial nerve palsy group, while in the non-cranial nerve palsy group, 36 (47.4%) patients had extracranial TB. In the cranial nerve palsy group, 19 (82.6%) cases had pulmonary tuberculosis. There were 14 (60.9%) cases of extrapulmonary tuberculosis: 5 (35.7%) cases had tuberculous pleurisy, 1 (7.1%) had tuberculous peritonitis, 1 (7.1%) had tuberculous pericarditis, 2 (14.3%) had bone tuberculosis, 1 (7.1%) had lymphatic tuberculosis, 3 (21.4%) had renal tuberculosis, and 1 (7.1%) had liver tuberculosis. Additionally, two (14.3%) patients had more than two sites of extrapulmonary TB (tuberculous pleurisy, tuberculous peritonitis, and liver

Table 4 Laboratory and Imaging Features in Patients of Tuberculous Meningitis with and without Cranial Nerve Palsy

Blood Tests							
N (%)	WBC↑	N↑	ESR↑	CRP↑	Hb↓	TB-Ab(+)	T-spot(+)
	27(23.6%)	82(71.9%)	38/86(44%)	25/53(47.2%)	33(28.9%)	45(45.5%)	22/33(66.7%)
Cerebrospinal fluid tests							
N (%)	Clear appearance	Cell count ≥50 (× 10 ⁶ /mL)	Protein ≥100mg/dL	Chloride↓	Intracranial pressure↑	Acid fast stain (+)	Csf/Blood glucose <0.5
	84(73.7%)	88/110(80%)	82(71.9%)	92(80.7%)	71(62.3%)	12(10.5%)	83/107(77.6%)
Imaging features							
N (%)	Hydrocephalus	Cerebral infarction	Meningeal reinforcement	Tuberculoma	EEG(+)	CXR(+)	
	36(31.9%)	57(50.4%)	74(66.1%)	12(10.6%)	53(75.5%)	52(46%)	

Note: Data are presented as n (%).

Abbreviations: ESR, E sedimentation rate (Reference range: Male 0–15mm/h, Female 0–20mm/h); CRP, C-reaction protein (Reference range: 0–8mg/L); Hb, Hemoglobin (Reference range: Male ≥120g/L, Female ≥110g/L); TB-Ab, Anti-tuberculous antibody; T-spot, T cell enzyme-linked immuno-spot assay; CSF WCC, Neutrophils and lymphocytes; EEG(+), Electroencephalogram anomaly; CXR(+), Chest radiograph suggestive of active tuberculosis signs of tuberculosis.

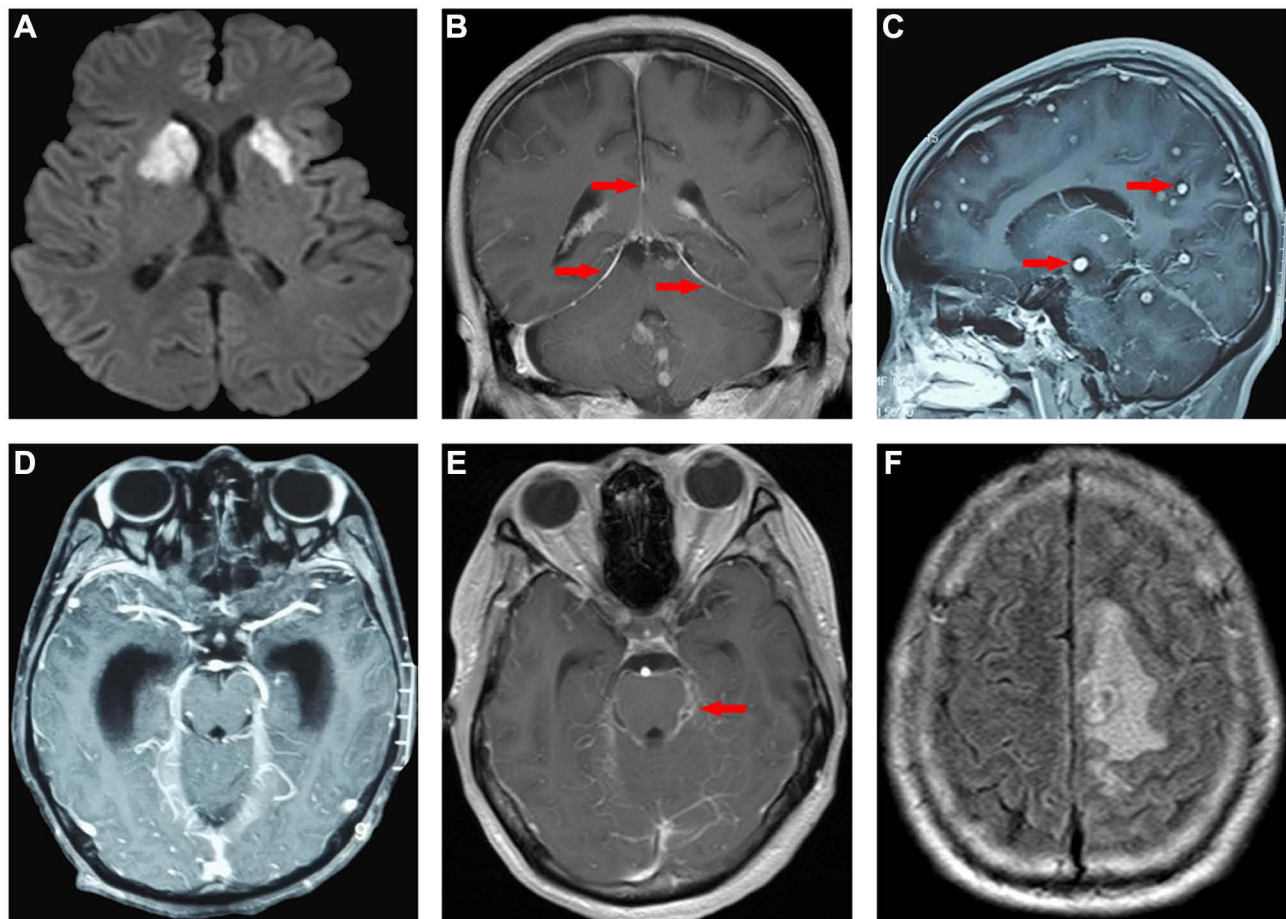


Figure 2 (A–F) Brain MRI scan abnormalities observed in tuberculous meningitis. **(A)** Diffusion-weighted image (DWI) showed acute infarction in bilateral basal ganglia. **(B)** Post-contrast MRI showed thickening and strengthening of the dura mater (arrows). **(C)** Post-contrast MRI showed multiple miliary tuberculosis (arrows). **(D)** Post-contrast MRI showed severe hydrocephalus secondary to TBM. **(E)** Post-contrast MRI showed basal meningeal enhancement (arrows). **(F)** MRI FLAIR sequence showed edema in the left frontal and parietal lobes.

tuberculosis in one case; tuberculous peritonitis, tuberculous pericarditis, and renal tuberculosis in another case) (see Figures 3–5).

Assessment of Factors Associated Cranial Nerve Palsy

Per univariate analysis, night sweats, headache, stiff-neck, altered consciousness, duration of illness, definite/probable TBM, focal neurological deficits, extracranial TB, anorexia, grade I/III, serum sodium, erythrocyte sedimentation rate,

Table 5 Various Patterns of Cranial Nerve Palsy in Patients with Tuberculous Meningitis

Nerve Affected	Number of Cases
2nd nerve	9
3rd nerve	19
6th nerve	2
8th nerve	1
2nd and 3rd nerve	2
2nd and 6th nerve	1
3rd and 6th nerve	2
9th and 10th nerve	1
2nd, 3rd and 8th nerve	1

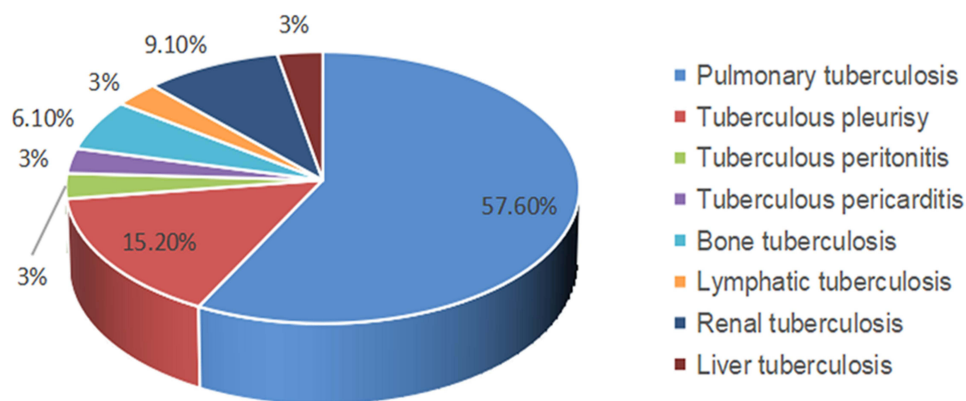


Figure 3 Evidence of TB elsewhere.

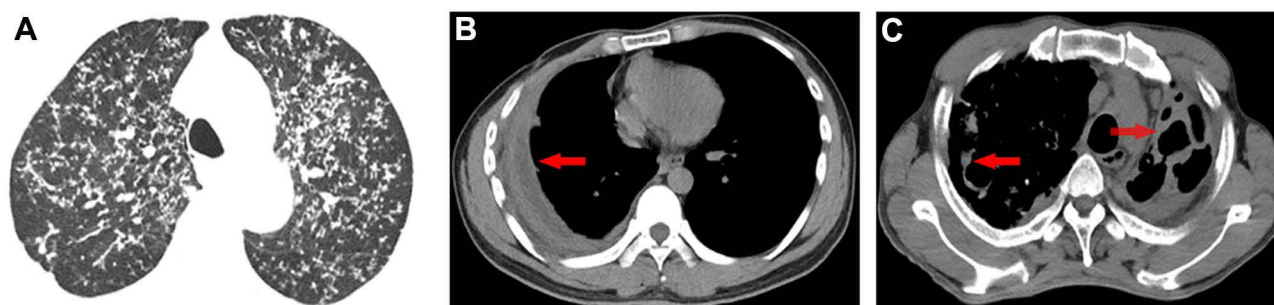


Figure 4 Type of TB. (A) CT showed pia miliary tuberculosis in both lungs. (B) CT showed marked pleural thickening at the right side (arrows). (C) CT showed bilateral pleural thickening and adhesion.

CRP, and CSF total WCC might be associated with cranial nerve palsy ($P < 0.2$) (see [Table 4](#)). A multivariate analysis model using binary logistic regression was then constructed and revealed that three factors (focal neurological deficits, extracranial TB, and CSF total WCC) were found to be associated with cranial nerve palsy (see [Table 6](#)).

Evolution of Cranial Nerve Palsy with Anti-TB Treatment

All study patients were treated with a standard four-drug anti-TB therapy (ATT), including isoniazid, rifampicin, pyrazinamide and ethambutol. Twenty-five (21.9%) patients received adjunctive corticosteroids (0.4 mg/kg/day of dexamethasone), and fluoroquinolones were used in combination in 45 patients (levofloxacin in 30 patients and moxifloxacin in 15). Moreover, patients were routinely treated with a combination of dehydration to reduce cranial pressure, and B vitamins to nourish the nerves whenever required.

All patients were followed up for 3 months after receiving anti-TB treatment to analyze the prognosis of cranial nerve palsy. If cranial nerve palsy persists or even worsens, or if death occurs, the patient is generally considered to have a poor prognosis in this regard. Both groups have paradoxical reactions during treatment. For non-cranial nerve palsy group: there were no deaths during follow up, 3 (3.9%) patients (1 patient with 2nd nerve, 1 patient with 3th nerve, and 1 patient with 6th nerve) had poor outcome. For cranial nerve palsy group: three patients died during the study period: one patient died due to a complication of foramen magnum hernia, one of infectious shock, and one of multiple organ failure; the final mortality rate was 7.9%. During the follow up of 35 patients who survived in the cranial nerve palsy group, 30 (85.7%) patients with cranial nerve palsy recovered completely, 3 (8.6%) experienced no change in vision, and 2 (5.7%) had deterioration in their hearing and swallowing status. For this group, 8 (21%; including 3 deaths) had poor outcome. In conclusion, the prognosis of non-cranial nerve palsy group was better than that of cranial nerve palsy group ($\chi^2 = 6.65$, $P = 0.01$) (see [Figures 1](#) and [6](#)).



Figure 5 MRI showed tuberculosis of L2 and L3 vertebrae (arrows).

Discussion

The main findings of this study were as follows: 1) cranial nerve palsy was a common complication, with an incidence of 33.3% in TBM patients; 2) auditory nerve, glossopharyngeal nerve, and vagus nerve palsies were rare, and most cases affected the oculomotor nerve, optic nerve, and abducens nerve; 3) after 3 months of follow-up, the majority of patients with cranial nerve palsy recovered completely with no obvious sequelae; and 4) cranial nerve palsy was associated with focal neurological deficits, extracranial TB, and CSF total WCC.

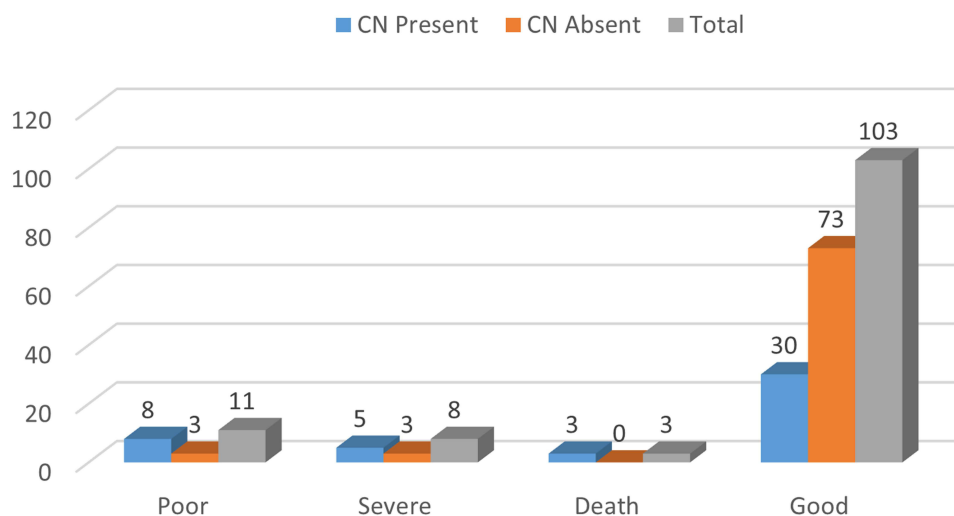
Table 6 Multivariate Logistic Regression Analysis

Variables	β -Coefficient	Standard Error (SE)	Odds Ratio (95% CI)	P value
Focal neurological deficits	5.779	2.199	323.428(4.344–24,078.682)	0.009
Extracranial TB	3.154	1.381	23.423(1.564–350.861)	0.022
CSF total WCC	0.011	0.005	1.011(1.000–1.021)	0.040

TBM is a devastating infection that occurs secondary to TB in areas other than the brain, is associated with the highest rate of mortality and disability,^{14–16} and is often complicated by cranial nerve palsy; however, its incidence has been reported inconsistently.^{9,10,17} In a study from India, Sharma et al enrolled 158 patients with TBM and found that cranial nerve palsy was present in 38% of patients with TBM. The abducens nerve was found to be the most common cranial neuropathy (32.3%), with two or more cranial nerve palsies in 10.12% of patients.¹⁰ A study by Li et al reported that the involvement of TBM with cranial nerve palsy was observed in only 14.8% of patients during follow-up. The oculomotor nerve palsy (56.9%) was the most common among these.⁹ In this study, cranial nerve palsy was detected in 33.3% of enrolled patients: the oculomotor nerve (the 3rd nerve) was the most frequently affected cranial nerve (52.2%), followed by optic nerve (the 2nd nerve) (28.3%), the abducens nerve (the 6th nerve) (10.9%), the auditory nerve (the 8th nerve) (4.3%), glossopharyngeal nerve (the 9th nerve) (2.2%), and the vagus nerve (the 10th nerve) (2.2%). 18.4% of cases had two or more groups of cranial nerve palsies. Finally, cranial nerve palsy was recovered at discharge in 30 (85.7%) patients.

The mechanisms attributed to the processes of cranial nerve palsy in TBM include the following. Firstly, MTB causes exudative and proliferative lesions in the CNS. The exudate deposits in the subarachnoid space at the bottom of the brain and the lateral cistern, which spreads around the brain stem and compresses the cranial nerve palsy. Second, CSF circulation suffers interference, resulting in ventricular orifices and aqueduct stenosis, and leading to obstructive hydrocephalus. Conversely, the excessive secretion of CSF brings about communicating hydrocephalus, causing the cranial nerve to be pulled and producing paralytic. Third, sometimes occlusive vasculitis leads to cerebral stem infarction and stroke, causing cranial nerve damage. Fourth, direct placeholder effect of cranial nerve in subarachnoid space by tuberculoma or abscess could be a mechanism. Fifth, intracranial hypertension and cerebral hernia can also damage the cranial nerves in advanced patients.

Extracranial TB was found to be an independent predictor of cranial nerve palsy. In the course of the initial pulmonary infection, MTB may enter the circulatory system and then reach the oxygen-rich CNS, where it seeds and forms a localized lesion, known as a “Rich foci”.¹⁸

**Figure 6** Effect of cranial nerve palsy of functional outcome after 3 months of follow up.

It may be located in the meninges, spinal cord, and brain parenchyma below the pia meninges or ependymal. Later, the lesion may rupture into the subarachnoid space or ventricle system leading to TBM.^{19,20} The probability of MTB reaching the brain depends on the degree of bacteremia and the host's immune response to it.^{21,22} Cell-mediated immune response in the brain produces a thick, gelatinous, inflammatory exudate, often involving the basal cistern and lateral fissure pools,²³ located in the basal cistern exudation can cause obstruction of CSF circulation leading to hydrocephalus and oppressive nerve,²⁴ and located at the base of the brain blood vessels serious involvement can lead to obstructive vasculitis and cerebral infarction.^{17,25–27} In addition, if the patient with TBM lacks adequate immunity or the lesion is large enough, foci of tuberculosis located in the brain parenchyma may develop into tuberculoma or brain abscesses.^{27–29}

CSF total WCC was significantly elevated in patients with cranial nerve palsy, suggesting an associated between the two. The high cell count of CSF total WCC could have caused the accumulation of inflammatory exudate and filling of the cistern with granulation tissue, which gradually developed into meningeal thickening and cerebral cistern casting enhancement, eventually leading to cranial nerve palsy.^{23,29}

The results of this study highlight the importance of focal neurological deficits as predictors of cranial nerve palsy. Focal neurological deficits were found in 50% of our enrolled patients. A previous study has observed that the enhancement of exudative meningitis of the circle of Willis in TBM can cause vascular strangulation, cramping, narrowing, periarteritis, and even necrotizing arteritis, leading to thrombosis.³⁰ Misra et al also found that focal weakness and cranial nerve palsy are predictors of persistent neurological sequelae.³¹ Another study reported that focal motor deficit at admission is also an important predictor of cranial nerve palsy.⁸

A previous study showed that cranial nerve palsy has a positive predictive role in the diagnosis of TBM and is the most important factor to differentiate TBM from acute bacterial meningitis.⁸ In terms of distribution, cranial nerve palsy was mainly in the anterior cranial nerve group, of which the oculomotor nerve was the most frequently involved cranial nerve, followed by the optic nerve and abducens nerve. Cranial nerve palsy in the posterior cranial nerve group was rare, which was consistent with several publications.^{8,9}

In our study, the incidence of cranial nerve palsy in patients with grade III (47.4%) was higher than that in patients with grade II (31.5%) or grade I (21.1%). This is consistent with the conclusions of Sher et al.³² It has been speculated that patients with severe TBM may be more prone to cranial nerve palsy. After admission, all patients underwent anti-TB treatment. Finally, cranial nerve palsy was almost resolved (85.7%) at the 3 months follow-up in the group of 38 patients. This result is similar to that reported by Li et al.⁹ Surprisingly, in a study from India,⁷ in a cohort with a high incidence of cranial nerve palsy, 10.2% of 88 TBM patients were blind and 12.5% experienced visual loss, which may be related to the longer average duration of illness (51±52 days vs 20±23.5 days) compared to this study. This further suggests that early diagnosis and intervention of TBM are of greatly important in alleviating or even reducing the sequelae of cranial nerve palsy.

Limitations

There were still some limitations in the present study. Firstly, our study was a retrospective two-center design. Information about enrolled patients was limited to medical records, which inevitably led to selective bias. Secondly, we were unable to assess the long-term prognosis of patients. Another limitation of this study is that PCR testing was not performed, which is considered important for accurate diagnosis of TBM. Fourthly, no patients with HIV were included. With these limitations considered, the subsequent step was to conduct a multicenter prospective cohort study in the region.

Conclusion

In summary, cranial nerve palsy is a common clinical complications of TBM, and focal neurological deficits, extracranial TB, and CSF total WCC are common predictors of cranial nerve palsy. In most patients with TBM, TBM-combined cranial nerve palsy is reversible and can be completely treated with effective anti-TB treatment. Clinicians should look for the clues of TBM and cranial nerve palsy carefully, as rapid and accurate diagnosis and effective treatment are the important means to reduce the occurrence of palsy and the resulting damage.

Data Sharing Statement

The original data supporting the conclusions of this paper will be provided by the authors, with no unnecessary reservations for any qualified researcher.

Ethical Statement

This study was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (NO.2022038). The study complied with the Declaration of Helsinki. Owing to the retrospective nature of the study, we only reviewed the medical records and all identifiable personal information was removed for privacy protection. So, patient consent for inclusion was waived.

Acknowledgments

The authors thank the staffs from the Neurology ward of Jiangxi Provincial People's Hospital for technical assistance as well as Editage (www.editage.cn) for English language editing.

Funding

This work was supported by grant from Jiangxi Provincial Health Commission Foundation (NO. 202310122).

Disclosure

The authors report no conflicts of interest in this work.

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