International Journal of Infectious Diseases 79 (2019) 104–108

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Paradoxical reaction in HIV-negative tuberculous meningitis patients with spinal involvement

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ARTICLE INFO

Article history:
Received 10 August 2018
Received in revised form 26 November 2018
Accepted 27 November 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculous meningitis
Spinal
Paradoxical reaction
Cerebrospinal fluid

ABSTRACT

Objective: The aim of this study was to investigate the occurrence of paradoxical reaction (PR) in HIV-negative tuberculous meningitis (TBM) patients with spinal involvement, as well as its possible risk factors.
Methods: Fifty TBM patients with spinal involvement were studied retrospectively and divided into a PR group and a non-PR group according to the presence of PR. Their demographic, clinical, radiological, and laboratory data, and status at follow-up were collected and compared.
Results: PR developed in 26 patients (52%), with the median time to the development of PR being 30 days (range 15–330 days) after the initiation of tuberculosis therapy. At initial diagnosis, age, documented acid-fast bacilli (AFB), and the cerebrospinal fluid protein level were found to differ significantly between the two groups. After multivariate analysis, age, documented AFB, and vertebral involvement were significantly associated with the development of PR.
Conclusions: PR was common in TBM patients with spinal involvement. Age, documented AFB, and musculoskeletal involvement may be predictors of PR development.

Introduction

Mycobacterium tuberculosis (TB) infection is responsible for a significant medical burden globally (Cheon et al., 2016; WHO, 2017; Gupta and Kumar, 2011). As stated by WHO in 2017, TB was the ninth leading cause of death worldwide, but the leading cause of death from a single infectious agent, ranking higher than HIV/AIDS. In 2016, about 10.4 million people fell ill with TB (WHO, 2017). TB deaths among HIV-negative people were estimated to be 1.3 million (down from 1.7 million in 2000). From 1990 to 2010, the prevalence of smear-positive TB in China decreased from 170 cases per 100 000 population (95% confidence interval (CI) 166–174) to 59 cases per 100 000 population (95% CI 49–72) (Wang et al., 2014). In addition, TB incidence in China in 2007 was estimated at 110 000 incident cases (95% CI 97 000–130 000) of multidrug-resistant (MDR)-TB and 8200 (95% CI 7200–9700) of extensively drug-resistant (XDR)-TB (Zhao et al., 2012). China continues to rank high among regions experiencing epidemics of both new-onset TB and MDR-TB (WHO, 2017).

In general, the incidence of central nervous system (CNS)-TB is directly proportional to the incidence of tuberculous infection, and this has been estimated to affect 10% of TB patients, more often younger patients (Garg, 1999). Despite the availability of effective anti-TB therapy, CNS-TB accounts for 1.5% to 3.2% of all TB-related deaths (Rock et al., 2008) and can result in significant neurological disability. Approximately 70–80% of all patients with neuro-tuberculosis have tuberculous meningitis (TBM) (Gupta and Kumar, 2011; Garg, 1999; Rock et al., 2008). Spinal involvement in TBM is a major cause of disability in CNS-TB and its presence significantly affects the prognosis. The mechanism of spinal involvement remains uncertain, but it is possible that tuberculous arachnoiditis leads to spinal involvement in CNS-TB (Gupta et al., 2015). Other pathogenic mechanisms (Wadia and Dastur, 1969a; Dastur and Wadia, 1969) may include hematogenous spread of mycobacteria to the spinal cord, gravitation of tuberculous exudate to the lumbosacral region, and perhaps rarely direct extension from vertebral TB. However, none of these have been studied

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https://doi.org/10.1016/j.ijid.2018.11.366

adequately. Indeed most of our understanding of TBM with spinal involvement is derived from case reports or small case series.

Paradoxical reaction (PR) in patients with TBM is characterized by either worsening of pre-existing tuberculous lesions or the onset of new tuberculous lesions in patients who have shown an initial improvement following anti-TB treatment. The clinical or radiological deterioration associated with such a reaction may suggest either a drug-resistant state or treatment failure, and may lead physicians to look for an alternative diagnosis (Afghani and Lieberman, 1994; Nicolls et al., 2005; Cheng et al., 2002). The influence of PR has not been studied in TBM patients with spinal involvement. Therefore, this retrospective study of a group of TBM patients with spinal involvement was performed to gain a better understanding of PR in TBM patients.

Patients and methods

Fifty TBM patients with spinal involvement, who were diagnosed and treated in the Third Xiangya Hospital and Central Hospital of Changsha City between September 2013 and September 2016, were studied retrospectively. Their average age was 41.5 ± 19.1 years; 32 were male and 18 were female. This study was approved by the Ethics Committee of the Third Xiangya Hospital, Central South University, and was conducted in accordance with the relevant guidelines.

Inclusion and exclusion criteria

According to the consensus diagnostic criteria described by Marais et al. (2010), all patients with definite or clinically probable TBM, with clinical or imaging proof of spinal involvement (including tuberculous spinal meningitis, arachnoiditis, myelopathy, radiculopathy, syrinx), were included. Definite cases were those in which direct evidence of acid-fast bacilli (AFB) in cerebrospinal fluid (CSF) was documented, by staining, culture, or commercial nucleic acid amplification tests. Probable TBM with spinal involvement were those cases that showed a diagnostic score of ≥12 when imaging was available and a diagnostic score of ≥10 when imaging was not available.

Patients with an infection of other confirmed cause or spinal diseases with other causes, such as spondylotic myelopathy or intervertebral disc protrusion, trauma, metastatic lesions, and other infections, were excluded from the study. Patients were also excluded when vertebral involvement was the sole spinal finding. Patients younger than 14 years old (treated in the pediatric department) or with incomplete clinical or imaging information were excluded.

A PR was defined as the worsening of pre-existing tuberculous lesions or CSF examination results, or the appearance of new tuberculous lesions in patients whose clinical symptoms had initially improved after at least 2 weeks of anti-TB treatment (Cheng et al., 2002). Patients were divided into groups based on the presence or absence of PR (PR group, non-PR group). It has been suggested that presumptive PR developing within 2–4 weeks of treatment initiation may be attributed to a delayed treatment response (Carvalho et al., 2006; Tai et al., 2016), and so PR manifestations were further compared in patients developing PR within and after 4 weeks of therapy initiation.

Clinical assessment

Demographic information, medications, history of tuberculous disease, and the presence of HIV infection and other systemic illnesses were recorded. Patients underwent general physical and neurological examinations. Patients were classified according to the British Medical Research Council (BMRC) staging system (Thwaites et al., 2004). BMRC grade 1 indicates a Glasgow coma scale (GCS) score of 15 with no neurological signs, grade 2 indicates a GCS score of 11–14 (or a score of 15 with focal neurological signs), and grade 3 indicates a GCS score of <10.

Laboratory investigations

Laboratory investigations were performed at baseline, including a complete hemogram, liver and renal function tests, erythrocyte sedimentation rate, C-reactive protein level, antibody to HIV, syphilis, and hepatitis virus (HBV and HCV). CSF analysis results were also collected for all patients, including routine examination, biochemistry, cytology, microbiology (including microscopy and culture for fungi and pyogenic bacteria), modified Ziehl–Neelsen stain, and *Mycobacterium tuberculosis* culture. Fluorescence quantitative PCR was performed to detect *M. tuberculosis* DNA and to determine susceptibility to rifampicin (RMP) and isoniazid (INH) in CSF. India ink staining and Cryptococcus latex agglutination testing (colloidal gold method, IMMY) were performed to rule out cryptococcal meningitis.

Neuroimaging findings

Brain and spine magnetic resonance imaging (MRI) examinations were done for each patient at baseline and after treatment, with neuroimaging definitions as follows (Singh et al., 2016). Hydrocephalus was defined as ventriculomegaly with an Evan's ratio (maximal width of frontal horns/maximal width of inner skull) of more than 30% and/or size of one or both temporal horns greater than 2 mm. Cerebrospinal meningeal inflammation was defined as a post-contrast enhancement of pia-arachnoid mater covering subarachnoid spaces of the sulci, basal cisterns, and spinal meninges. Spinal arachnoiditis was defined by the presence of enhancement of spinal meninges and nerve roots, obliteration of the spinal subarachnoid space, cysts and loculations in the subarachnoid space, or syrinx formation. Tuberculomas were defined as discrete or coalescing cerebral masses showing nodular or ring-shaped enhancement. Infarcts were areas of abnormal signal intensity in a vascular distribution, predominantly in periventricular regions. Infarcts appeared hyperintense on T2-weighted images and hypointense on T1-weighted images, with corresponding changes on diffusion-weighted and apparent diffusion coefficient images. MRI of the spine was reviewed for the presence of myelitis, lumbosacral arachnoiditis, CSF loculations, tuberculoma, cord atrophy, syrinx formation, and spinal meningeal enhancement. The extent of spinal involvement was assessed by the proportions of CSF signal alteration, contrast enhancement of the meninges, or clumping of nerve roots, whichever was more extensive. The presence of low signal intensity on T1-weighted imaging and high signal intensity in the corresponding region on T2-weighted imaging with a well-defined margin was taken as evidence of syrinx formation. Myelitis was identified by hyperintense signal on T2-weighted image associated with cord edema, enlargement, and marginal enhancement on contrast. MRI of the spine was repeated only for those patients who developed new symptoms suggestive of spinal cord and spinal nerve root involvement.

Treatment

At TBM diagnosis, patients were started on TB treatment according to national guidelines (Thwaites et al., 2004): INH (5 mg/kg/day; maximum 300 mg), RMP (10 mg/kg/day; maximum 600 mg), pyrazinamide (PZA; 25 mg/kg/day; maximum 2 g per day), and ethambutol (EMB; 20 mg/kg/day; maximum 1.2 g per day) for 3 months, followed by INH and RMP at the same doses for

an additional 6 months. All patients received adjunct treatment with intravenous dexamethasone (0.3–0.4 mg/kg/day) or equivalent methylprednisolone for the first 2–4 weeks of treatment, and then oral treatment with prednisone for 2–4 weeks, as described previously (Thwaites et al., 2004). Patients were also provided with appropriate symptomatic treatment (mannitol, antiepileptic drugs, analgesics, etc.) as required.

Follow-up

Clinical outcomes at the time of discharge and follow-up data for at least 9 months were graded using a modified Rankin score (MRS) (van Swieten et al., 1988), ranging from 0 (no symptoms) to 5 (totally dependent on others, requiring help day and night). These were classified as a 'good outcome' (a score of 0), 'intermediate outcome' (scores of 1 or 2), 'severe disability' (scores of 3, 4, or 5), or 'death'. Patients were assessed at monthly intervals. New neurological events were defined as the occurrence of any of the following: cerebellar symptoms; monoplegia, hemiplegia, paraplegia, or tetraplegia; seizures; cranial nerve palsy; a decrease in GCS score of 2 or more points for $\geq$2 days from the highest previously recorded score.

Statistical analysis

The Chi-square test (or Fisher's exact test) was used to analyze categorical data. Continuous variables were expressed as means and analyzed with the Student *t*-test. A *p*-value of <0.05 (two-tailed *p*-value) was considered statistically significant. Pearson's correlation was used for univariate analysis. Binary logistic regression analysis was performed for variables with $p < 0.20$ on univariate analysis, and results were considered statistically

Table 1
Comparison of baseline demographic and clinical symptoms between the paradoxical reaction (PR) and non-paradoxical reaction (non-PR) groups.[a]

	PR group $n = 26$	Non-PR group $n = 24$	*p*-Value
Age (years)	34.9 ± 18.1	48.6 ± 18.6	0.01
Sex, male	15	17	0.33
Duration of symptoms (days)	128.8 ± 251.6	42.0 ± 49.0	0.11
GCS score on presentation	13.3 ± 3.6	13.0 ± 3.0	0.68
MRS score	1.65 ± 1.72	2.5 ± 2.2	0.13
BMRC stage			
Stage 1	14	15	0.53
Stage 2	8	5	0.64
Stage 3	4	4	0.79
Clinical symptoms			
Tuberculous toxic symptoms	24	21	0.92
Fever	24	21	0.92
Headache	22	18	0.62
Vomiting	9	7	0.67
Cough	10	11	0.59
Neck rigidity	20	17	0.62
Seizures	1	3	0.54
Limb weakness	9	11	0.41
Sensory abnormality	8	12	0.42
Pathological signs	1	3	0.54
Urinary/constipation symptoms	13	9	0.37
Cranial nerve involvement	3	4	0.90
Consciousness alteration	14	11	0.57
Radiological findings			
Hydrocephalus	8	2	0.10
Interstitial edema	2	1	0.94
Brain meningeal enhancement	22	19	0.89
Tuberculoma	9	11	0.41
Cerebral infarct	1	1	1.00
Basal high intensity before enhancement	4	1	0.40
Spinal meningeal involvement	25	21	0.54
Myelopathy	15	9	0.15
Past history/comorbidity			
History of TB infection	3	5	0.61
DM	1	1	1.00
Previous use of immunosuppressant/steroids	5	1	0.19
Syphilis	0	1	0.48
Hepatitis virus	3	2	0.92
Hematogenous TB spread	9	5	0.28
Non-CNS extrapulmonary TB	13	7	0.13
Vertebral TB involvement	8	2	0.10
CSF			
Pressure (mmHg)	232.7 ± 129.6	220.4 ± 113.6	0.72
Cytological count (×106/l)	417.2 ± 485.9	474.8 ± 661.6	0.73
White cell count (×106/l)	288.9 ± 392.8	247.3 ± 358.5	0.70
Protein (g/l)	3.0 ± 1.6	2.1 ± 1.4	0.03
Glucose (mmol/l)	2.1 ± 1.2	2.7 ± 1.4	0.12
Chloride (mmol/l)	108.8 ± 22.3	112.7 ± 8.9	0.13
Positive AFB evidence	5	13	0.01

GCS, Glasgow coma scale; MRS, modified Rankin score; BMRC, British Medical Research Council; TB, tuberculosis; DM, diabetes mellitus; CNS, central nervous system; CSF, cerebrospinal fluid; AFB, acid-fast bacilli.

[a] Data shown as the mean ± standard deviation, or number.

significant with values of $p < 0.05$. All statistical analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Of the 50 patients examined in this study, 26 manifested a PR during treatment (PR group) and 24 patients were free of PR (non-PR group). Table 1 presents the baseline demographic information, clinical manifestations, imaging findings, laboratory investigations, and follow-up results.

Of the 26 patients with PR, imaging deterioration occurred in 21 patients, the CSF examination worsened in four patients, and development or progression of spinal symptoms occurred in six patients. The time to PR development ranged from 15 to 330 days (median 30 days). Six patients developed PR within 28 days after treatment initiation and 20 patients developed PR after 28 days; Table 2 shows a comparison of the characteristics of these two groups. Patients with PR developing at <28 days were significantly more likely to be younger and female than those who developed PR later. PR manifestations did not significantly differ based on time of onset.

Patient age was significantly lower and the baseline CSF protein level was significantly higher in the PR group than in the non-PR group, while documented AFB (positive finding of smear, culture, or PCR results) was significantly more frequent in the non-PR group. There were no other significant differences identified in clinical symptoms or imaging results.

On univariate analysis, patient age, CSF protein level, hydrocephalus, and documented AFB were significantly correlated with the development of PR, while multivariate analysis showed that only age, documented AFB, and vertebral involvement were significantly associated with the development of PR (Table 3). In addition, neither the occurrence of PR nor the studied variables mentioned above correlated with the follow-up MRS score in this group of patients (data not shown).

Discussion

This study retrospectively examined the occurrence of PR in a group of TBM patients with spinal involvement. PR in HIV-negative patients has been reported with varying frequency, ranging from <1% to 56% in the published literature (Garg et al., 2014). The occurrence of PR in extrapulmonary TB is higher than in the setting of pulmonary TB, with CNS infection having the highest occurrence rates (Garg et al., 2014). Similar to previous reports of PR in TBM patients, PR was a common finding during treatment, occurring in 52% of the patients studied.

In this study, age was significantly younger in the PR group than in the non-PR group. Age has been suggested to be an important predictor of the TBM prognosis in the previous literature (Misra et al., 1996); however, its correlation with the development of PR is not commonly reported. In previous studies on PR in TBM, only Olive et al. (2013) and Thampi et al. (2012) reported that age may be associated with the occurrence of PR (in studies on pediatric TB infection). As the mechanism of TBM in patients with spinal involvement remains unclear and sampling bias could not be excluded, the effect of age in the pediatric range is not clear. The present study excluded children aged <14 years. However, it was still found that younger age among the mostly adult population was a significant independent predictor of PR. Whether age does or does not play a role in the immune response to TB infection requires further investigation.

The mechanism of PR is still poorly understood. Beyond microbiological relapse, the development of paradoxical manifestations may result from a patient's exaggerated immune response to dead and dying bacteria (Tai et al., 2016; Garg et al., 2014; Olive et al., 2013; Thampi et al., 2012; Kim and Kim, 2009). In this study, young age and the lack of a documented pathogen presence might be interpreted as indicating a robust immune response towards TB, and thus may be predictive of PR development.

Further, as suggested in previous studies, PR occurring before and after 4 weeks of treatment may depend on different mechanisms (Tai et al., 2016; Sütlas et al., 2003; Ramesh et al., 2014). CSF changes were more frequent in those with PR developing within 4 weeks, and tuberculoma progression was more frequent in those with PR developing after 4 weeks of treatment (Sütlas et al., 2003; Ramesh et al., 2014). Thus, patients with PR development times of less than and more than 4 weeks were compared, and it was found that age and sex differed significantly between the two groups. In agreement with the previous literature, the manifestation of cerebral tuberculoma progression was significantly more frequent in patients with PR occurring at >4 weeks after treatment initiation. Due to the limited sample size, further studies are warranted with more details on CSF and imaging changes. In addition, the paradoxical manifestation may occur even after prolonged therapy, a fact that suggests the antigenic stimulus may be poorly cleared from disease sites (Hawkey et al., 2005). In this study, PR development occurred as late as 330 days after the initiation of therapy.

Spinal involvement in TBM may be common. Gupta et al. (2015) performed a prospective study and reported that 46.4% (30/71) showed spinal involvement, with spinal meningeal enhancement being the most common manifestation. However, imaging abnormalities might not necessarily correlate with clinical manifestations, as suggested by Srivastava and Kochar

Table 2
Comparison of patient subgroups with paradoxical reaction manifesting at <28 days vs. >28 days.

	Development time		*p*-Value
	<28 days *n* = 6	>28 days *n* = 20	
Age (years)	23.3 ± 9.6	38.4 ± 17.5	0.02
Sex, male	1	14	0.02
Time to PR development (days)	17.7 ± 2.7	124.2 ± 2.7	0.01
Clinical manifestation	1	5	0.67
Newly developed	0	1	1.00
Progression	1	4	1.00
Imaging manifestation	5	17	0.92
Cerebral tuberculoma increase	0	15	<0.01
Spinal tuberculoma/myelitis increase	3	10	1.00
Hydrocephalus progression	1	1	0.42
Meningeal enhancement progression	5	15	1.00
Vertebral lesion development	0	1	1.00
CSF manifestation	2	2	0.16
Protein elevation	2	2	0.21
Cytosis	2	1	0.12

PR, paradoxical reaction; CSF, cerebrospinal fluid.
[a]Data shown as the mean ± standard deviation, or number.

Table 3
Risk factors for paradoxical reaction development in tuberculous meningitis with spinal involvement.

	Univariate analysis		Multivariate analysis	
	R	*p*-Value	OR (95% CI)	*p*-Value
Age	−0.359	0.01	0.92 (0.86–0.98)	0.01
CSF protein	0.305	0.03	1.18 (0.70–1.97)	0.53
AFB documented	−0.364	<0.01	0.18 (0.03–0.93)	0.04
Hydrocephalus	0.280	<0.05	3.23 (0.45–23.14)	0.46
Vertebral involvement	0.280	<0.05	34.77 (2.19–447.72)	0.01

OR, odds ratio; CI, confidence interval; CSF, cerebrospinal fluid; AFB, acid-fast bacilli.

(2003) and Wadia and Dastur (1969b). Similarly, in the present study, it was found that spinal meningeal enhancement was the most common manifestation in TBM patients with spinal involvement. However, instead of hematogenous TB dissemination, vertebral involvement was found to be significantly associated with PR development in this study. Therefore, it is speculated that dissemination routes may be important in eliciting different immune responses to TB infection, as CNS-TB may be highly compartmentalized (Thuong and Thwaites, 2017).

Prompt and effective treatment has greatly improved the prognosis of TBM patients with spinal involvement, and none of these patients showed drug resistance. Serum therapeutic drug monitoring (TDM) was not employed in these patients, as it is mainly used in the treatment of MDR/XDR-TB and its clinical utility in CNS-TB is controversial. In this study, all patients received corticosteroids for 1 month. However, PR most frequently developed after 1 month, thus corticosteroid administration for patients with PR varied depending on clinical severity. Among the patients with PR, 12 with obvious clinical and/or imaging deterioration received further corticosteroids, and all of them showed a significant improvement. Although frequently suggested in the previous literature (Garg et al., 2014), the indication, optimal dose and duration, and effect of corticosteroid in CNS-TB patients with PR still need to be confirmed in more randomized trials. In addition, none of the patients died, and the average MRS score did not differ significantly between the two groups. Based on multivariate analysis, PR was not significantly associated with the prognosis in TBM patients with spinal involvement, similar to previous publications regarding TBM. However, it was also observed that patients with PR tended to require multiple admissions for in-hospital treatment and had a more expensive treatment course due to fluctuating symptoms than patients without PR (data not shown).

Elevated CSF protein has been suggested to be a risk factor for the development of spinal arachnoiditis in CNS-TB patients. Gupta et al. (2015) suggested that high CSF protein (>250 mg/dl) was an important predictor associated with myeloradiculopathy. In the present study, CSF protein was found to be significantly higher in the PR group than in the non-PR group. However, it was not significantly correlated with the onset of PR or associated with clinical symptoms, possibly because the CSF protein levels in this study were relatively low overall. This finding also indicates that spinal involvement may be more common than expected, and spine MRI investigation should be performed, especially in cases with high CSF protein levels, to reveal the spinal involvement status for timely treatment and improved outcomes.

The retrospective nature of this study and small sample size limit the generalizability of the results. Not all patients in this study with PR received corticosteroids. This may add bias to the outcome analysis, although baseline data were mainly analyzed. In the future, a prospective study with more strict inclusion criteria should be performed.

In conclusion, PR was common in TBM patients with spinal involvement, and neuroimaging progression may be the most common manifestation. Age, pathological findings, and vertebral involvement may be predictors of PR development.

Acknowledgements

We acknowledge the patients and their families, and the staff at the Third Xiangya Hospital, Central South University and Changsha Central Hospital, as well as members of the laboratory of the Department of Neurology, the Third Xiangya Hospital, Central South University.

Funding

This work was supported by the New Xiangya Talent Projects of the Third Xiangya Hospital of Central South University (JY201613).

Conflict of interest

All authors report no conflicts of interest.

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