Predictors of long-term neurological sequelae of tuberculous meningitis: a multivariate analysis

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There is paucity of studies on predictors of long-term sequelae of tuberculous meningitis (TBM). We report the neurological sequelae of TBM at 1 year and their predictors. Patients with TBM who were followed up for 1 year were included. The diagnosis of TBM was based on clinical, cerebrospinal fluid (CSF) and computed tomography (CT) scan findings. Detailed neurological examinations at admission and at 1 year were carried out. All the patients received four-drug antitubercular therapy. The frequency of sequelae at 1 year were noted and the role of various demographic (age, sex, duration of illness, BCG vaccination), clinical (weakness, seizure, extra central nervous system tuberculosis, Glasgow Coma Scale (GCS) score, cranial nerve palsy, stage, corticosteroid, drug-induced hepatitis, shunt surgery), and laboratory findings (erythrocyte sedimentation rate (ESR), CSF cell and protein, CT scan evidences of hydrocephalus, basal exudates, infarctions and tuberculoma) at presentation were evaluated employing logistic regression analysis. Sixty-five patients with TBM were included in this study whose age ranged between 13 and 80 years (mean 33.2), 27 of whom were females. Complete neurological recovery at 1 year occurred in 21.5% patients only although about 50% were independent for activities of daily living. Neurological sequelae were observed in 78.5% patients, which included cognitive impairment in 55%, motor deficit in 40%, optic atrophy in 37% and other cranial nerve palsy in 23%. On logistic regression analysis, focal motor deficit at admission was the most important predictor of neurologic deficits at 1 year. GCS score predicted the cognitive and motor sequelae. Neurological sequelae at year occurred in 78.5% patients with TBM in the form of cognitive impairment, motor deficit and optic atrophy. Sequelae were common in patients who had focal motor deficit and altered sensorium at admission.

Introduction

Tuberculous meningitis (TBM) is the commonest cause of chronic meningitis and is not only prevalent in the developing countries but also is being reported from the developed countries because of emergence of AIDS, organ transplantation and increasing use of immunosuppressants. The availability of effective, central nervous system (CNS) penetrating antitubercular drugs and computed tomography (CT) scan has contributed to better management and early diagnosis of hydrocephalus resulting in steep decline in mortality of these patients. This has been however paralleled by a steep rise in number of survivors with varying degree of neurological deficits. Neurological sequelae such as hemiplegia, quadriplegia, cognitive impairment, seizures and cranial nerve palsy have been reported in 25–56.1% of survivors [1–5]. The occurrence of neurological sequelae has been attributed to duration of illness, stage of meningitis and extremes of age [1,2,6–8]. In these studies, CT scan was not done in all the patients and treatment protocol was heterogeneous. In the post-CT scan and magnetic resonance imaging (MRI) era age, coma, stage of TBM, associated military tuberculosis, hydrocephalous, infarctions and basal exudates are reported as poor prognostic predictors [9–13]. We have reported prognostic predictors of TBM [10,14]. In these studies the outcome was assessed on the basis of Barthel Index (BI) score but detailed neurological deficits at 1 year were not evaluated. There is no comprehensive prospective study in the medical literature evaluating the pattern of neurological sequelae at 1 year in TBM and their predictors employing multivariate analysis. A retrospective study of TBM reported neurologic sequelae in 27%, which included cranial nerve palsy, monoparesis, hemiparesis and amnesia [15]. In the present communication, we report the

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pattern of neurological sequelae at 1 year and its pre-dictors.

Patients and methods

Patients with TBM who have been prospectively fol-lowed up for 1 year were included in this study. A de-tailed neurological evaluation was carried out at admission. Consciousness was assessed by Glasgow Coma Scale (GCS). Cranial nerve palsy, muscle power, tone and reflexes were noted. Cerebellar signs and sensations were also assessed in the patients who could cooperate. Plain and contrast cranial CT scan was carried out and 10 mm axial sections were obtained parallel to orbitomeatal line. Presence of exudates, in-farctions, hydrocephalus and tuberculoma was noted.

The diagnosis of TBM was based on clinical, CT scan and CSF criteria. The essential criteria included pres-ence of meningitic symptoms comprising fever, head-ache and vomiting for 2 weeks or more in whom malaria, septic, fungal and carcinomatous meningitides were excluded. The supportive criteria included (i) CSF cells 0.2×10^9/l or more with predominant lympho-cytes, protein more than 2 g/l, sterile bacterial and fungal culture; (ii) CT scan evidences of exudates, in-farctions, hydrocephalus and tuberculoma in various combinations; (iii) evidence of extra CNS tuberculosis and (iv) response to antitubercular therapy. Presence of essential and three of four supportive criteria was considered suggestive of TBM [14]. Positive PCR for mycobacterium TB or IgM ELISA (immunoglubulin M enzyme-linked immunosorbent assay) or acid fast bacilli (AFB) in CSF smear or culture was considered definitive evidence of TBM. Serum ELISA for HIV was carried out in all. The severity of meningitis was graded as stage I: meningitis only, stage II: meningitis with focal neurological signs and stage III: meningitis with altered sensorium [16]. Patients were treated with four-drug antitubercular (rifampicin 10 mg/kg, isoniazide 5 mg/kg, pyrazinamide 25 mg/kg and ethambutol 15 mg/kg) daily regimen. All four drugs were continued till 8 months followed by three drugs (isoniazide, rif-ampicin and ethambutol) till 12 months following which two drugs (isoniazide and ethambutol) were continued for a total duration of 18 months. Predn-isolone (0.5–1 mg/kg) was prescribed only to the patients with encephalopathy, raised intracranial pres-sure and impending visual failure for a period of 1 month followed by rapid taper in the next month. Ventriculoperitoneal shunt was carried out if there was raised intracranial pressure with features of herniation caused by obstructive hydrocephalous. In patients with communicating hydrocephalous with features of raised intracranial pressure, repeated CSF drainage by lumbar puncture was tried before subjecting them to shunt surgery. Functional outcome was defined on the basis of 1-year 0–20 BI score [17] into poor (BI < 12), partial (BI = 12–19) and complete (BI = 20) recovery [10].

For documenting the neurological sequelae, patients were followed up personally at 1 year of therapy. They were evaluated for cognitive impairment employing Mini Mental State Examinations (MMSE). Patients were considered cognitively impaired if MMSE score was below 29 for 9 years of schooling, below 26 for 5–8 years of schooling and below 22 if 0–4 years of schooling [18]. Presence of visual impairment, optic atrophy and other cranial nerve palsy was noted. For sensory motor deficit a detailed examination including pinprick, joint position and vibration sensations, mus-cle power, tone, reflexes and cerebellar signs were done.

Statistical analysis

Neurological deficits at 1 year were correlated with various clinical, laboratory and CT scan parameters at admission using chi-square, Fisher's exact or inde-pendent t-test. The predictors of neurological deficit, cognitive impairment, optic atrophy, and motor deficit at 1 year were evaluated separately employing logistic regression analysis in SPSS software [version 10; 19]. The independent variables were categorized as follows: sex (male = 0, female = 1), focal motor deficit, sei-zures, extra CNS tuberculosis, cranial nerve palsy, hydrocephalus, infarction, exudates, tuberculoma, drug-induced hepatitis, BCG vaccination, steroid and shunt surgery (yes = 1, no = 0) and stage (stage I = 1, stage II = 2, stage III = 3). The raw score of age, duration of illness, GCS score, ESR and CSF cell and protein were used. The dependent dichotomous varia-bles neurological deficit, cognitive impairment, optic atrophy, and motor deficit were assigned the value 0 when absent and 1 when present.

Results

During last 4 years, we treated 90 patients with TBM. Eight patients died during hospital stay, two had associated HIV and 15 patients did not complete 1-year follow-up. The results therefore are based on 65 pa-tients. Their mean age was 33.2 years (13–80) and 27 of them were females. The duration of illness ranged be-tween 0.5 and 16 months (mean 6). The antitubercular therapy was started within 1–7 days of hospitalization. Extra CNS tuberculosis was present in 17 patients, which included pulmonary tuberculosis in 14 (six mil-itary), Pott's spine in two and tubercular lymphadeno-pathy in one. Acid fast bacilli in CSF smear or culture was present in four, positive PCR in 13 and IgM ELISA

in 33 patients. None had multi-drug resistance tuberculosis and HIV. Twenty-four patients received BCG vaccination. Majority had severe meningitis; 36 patients were in stage III, 15 in stage II and 14 in stage I. The mean GCS score was 11.6 (range 4–15). Six patients were deeply comatose (GCS < 6), 20 moderately (GCS 6–12) and 10 had mild alteration of sensorium. Seizures occurred in 21 patients, which were generalized tonic-clonic in five, partial motor in two and partial motor with secondary generalization in 14 patients. In these patients seizures were controlled with phenytoin monotherapy. Ophthalmoplegia was present in 13 and impaired hearing in two patients. Focal motor deficit was noted in 26 patients; hemiparesis in 16, paraparesis in four and quadriparesis in six. Three patients had cerebellar ataxia and none received antiepileptic drugs or streptomycin.

Cranial CT scan at admission was abnormal in 59 patients and revealed hydrocephalus in 30 (communicating in 25 and obstructive in five), exudates in 22, tuberculoma in 20 (supratentorial in 14, infratentorial in six) and infarctions in 16. The infarctions were multiple small located in subcortical area in all except two who had large cortical and pontomedullary infarctions.

One-year follow up

Thirty-three patients had complete, four partial and 28 poor recovery at the end of 1 year on the basis of BI score. The neurological deficits at 1 year however were quite common occurring in 51 patients and included cognitive impairment in 36, optic atrophy in 24, other cranial nerve palsy in 15 (ophthalmoplegia in 13, hearing deficit in two), hemiparesis in 11, paraparesis in four, quadriparesis in 11 and ataxia in three. Thirteen patients had hyporeflexia raising a possibility of spinal meningitis; however, spinal MRI or CT myelogram was not carried out. None of the patients had recurrences of seizure. The MMSE score in the patients with cognitive impairment ranged between 6 and 28 (mean 22). MMSE score was < 19 in seven patients, 19–24 in six and remaining had mild cognitive impairment. Presence of optic atrophy resulted in severe visual impairment in 11 patients; three of them had no perception of light and eight no perception of finger movement. Moderate to severe (Medical Research Council (MRC) grade ≤3) hemiparesis was present in four, quadriparesis in 10 and paraparesis in four patients. The remaining had mild weakness. Patients with ataxia were able to walk with support. Steroid therapy was not related to occurrence of neurologic sequelae ($P = 0.35$). Eighty two percent of TB meningitis patients on steroid therapy and 71% without steroid therapy had neurological sequelae.

Focal motor deficit at admission ($P = 0.03$) and vaccination ($P = 0.03$) significantly related to neurologic sequelae at 1 year on Fisher's exact test but on regression analysis only focal motor deficit (Odds Ratio, 5.33; 95% Confidence Interval: 1.08–26.27, $P = 0.04$) was the predictor of sequelae. Level of consciousness as assessed by GCS score was the most significant predictor of cognitive impairment (OR 0.76, 95% CI: 0.62–0.94, $P = 0.01$) and motor deficit (OR 0.83, 95% CI: 0.70–0.99, $P = 0.03$). On regression analysis for optic atrophy no significant variable could be identified although higher number of patients with cranial nerve palsy at admission developed optic atrophy ($P = 0.05$). Twenty-two of 24 patients with optic atrophy had papilloedema and 11 each had basal exudates and hydrocephalous; whereas 19 patients with hydrocephalous and 15 with basal exudates did not have optic atrophy. The relationship of optic atrophy with hydrocephalous ($P = 1.00$) and basal exudates ($P = 0.60$) was not significant. The significant variables predicting the various sequelae of TBM and their break up are presented in Table 1.

Table 1 Variables related to neurological sequelae at 1 year

	Present	Absent	P value
Neurological deficit	n = 51	n = 14	
Focal motor deficit			
Present	24 (92%)	2 (8%)	0.03
Absent	27 (69.2%)	12 (30.9%)	
BCG vaccination			
Yes	15 (62.5%)	9 (37.5%)	0.03
No	36 (87.8%)	5 (12.2%)	
Cognitive impairment	n = 36	n = 29	
Focal motor deficit			
Present	19	7	0.02
Absent	17	22	
GCS score	11.58 ± 3.52	13.69 ± 1.91	0.005
Shunt			
Present	12	0	0.001
Absent	24	29	
Optic atrophy	n = 24	n = 41	
CN palsy	11 (57.9%)	8 (42.1%)	0.05
No CN palsy	13 (28.3%)	33 (71.7%)	
Motor deficit	n = 26	n = 39	
Focal motor deficit+	19 (73.1%)	7 (17.9%)	0.0001
Focal motor deficit−	7 (26.9%)	32 (82.1%)	
GCS score	11.5 ± 3.46	13.21 ± 2.63	0.03
Stage			
I	5	9	0.03
II	2	13	
III	19	17	
Shunt			
Present	9	3	0.01
Absent	17	36	

CN, cranial nerve; GCS, Glasgow Coma Scale.

Discussion

In our study neurological sequelae were noted in 51 (78.5%) of 65 survivors of TBM at 1 year and included cognitive impairment (55%), motor deficit (40%), visual impairment (37%) and other cranial nerve palsy (23%). In an earlier series on children treated without isoniazide, 64% of survivors were completely normal, 21% had mild to moderate neurological deficit and 15% had eighth cranial nerve deficit, which was attributed to streptomycin [20]. Other studies reported moderate to severe neurological sequelae in 25–50% children treated with isoniazide [1,2]. In adults, percentage of neurological handicaps varies from 0% to 56.1% of survivors [5–7,15,21,22]. In our study, mild to severe neurological sequelae were noted in about 78.5% patients although 50% of patients were independent for activities of daily living. The higher percentage of neurological sequelae in our study may be due to different patient population, inclusion of more severely ill patients and referral bias. Ours is a tertiary care referral centre which results in referral of serious patients; 51 of 65 patients were in stage III or II meningitis. Amongst the neurological sequelae in children, the commonest was spastic hemiparesis followed by seizure disorder, ataxia and rarely cranial nerve palsy [23,24]. Children needed longer hospital stay due to their cognitive and emotional impairment [20,25]. In adult survivors, most frequent sequelae of TBM has been described as organic brain syndrome followed by cranial nerve palsy, paraparesis and hemiparesis [22,26]. Optic atrophy has been noted both in children and adults [27–29]. These studies were carried out mostly before the rifampicin and pyrazinamide era. Inspite of four-drug antitubercular therapy in our study also cognitive impairment was a dominant sequelae followed by motor deficit and optic atrophy. In a recent study, 56.1% patients developed minor to major neurological sequelae despite modern antitubercular treatment. In this study poor outcome was attributed to advanced disease and positive *Mycobacterium tuberculosis* in CSF culture [5]. Other rare complications of TBM such as diabetes insipidus, chronic hypothermia, hypopituitarism, precocious puberty were not found in our patients.

The sequelae of TBM have been reported to correlate with stage of meningitis at admission. Patients treated in early stage are five times more likely to recover completely than those with advanced disease [20]. Younger patients have been reported to have more severe neurological sequelae especially below 2 years of age [1,2]. These studies were based on univariate analysis taking heterogeneous patient population. The sequelae were defined qualitatively and CT scan findings were not included. The present study is a prospective evaluation of neurological sequelae of patients with TBM without above-mentioned limitations. In TBM, various pathological changes such as meningeal adhesion, infarction, tuberculoma and hydrocephalus may occur simultaneously in the same patient influencing the subsequent sequelae. Low GCS and focal neurological deficits at presentation suggest a more severe illness. None of the radiological parameters were found to be significant predictor of sequelae. In TBM, infarctions are small and involve deep white matter, basal ganglia and thalamus. Strategic location of these infarctions may result persistent weakness as shown in our earlier study on stroke [30]. Motor deficit in TBM may also be contributed by adhesive arachnoiditis resulting in myeloradiculopathy. Thirteen of our patients had hyporeflexia suggesting possible spinal components in the genesis of motor deficit; however, spinal MRI or CT myelogram was not carried out. Altered sensorium in TBM may be due to associated encephalitis, hydrocephalus and infarctions. Hydrocephalus in TBM is mostly communicating and if it stabilizes following treatment may not be responsible in isolation for long-term motor or cognitive deficit. Optic nerve in TBM may be involved because of raised intracranial pressure, hydrocephalus, exudates and vasculitis. More number of patients with optic atrophy in our study had cranial nerve palsy at presentation, which may be due to basal meningitis or raised intracranial pressure. BCG-vaccinated patients had lesser frequency of neurological sequelae. Vaccination has been reported to reduce the severity and complications of tuberculosis [31]. In a 20-year retrospective study of 38 children with CNS tuberculosis, permanent neurological sequelae were seen in 47%. None of the children who received BCG vaccination had permanent neurological sequelae. Mortality and morbidity were higher in younger children (< 10 years) and stage III meningitis [32]. Steroid although has been reported to reduce the neurological sequelae [33] but it did not show any impact neither in the present study nor in our earlier study [34]. In a randomized controlled trial, steroid did not have any influence in the occurrence of motor deficit, blindness and deafness in 141 children with TBM [35].

It can be concluded that complete functional recovery although occurs in 50% patients with TBM at 1 year but complete neurological recovery occurs in 21.5% patients only. Altered sensorium, motor deficit, lack of BCG vaccination, stage of meningitis and shunt surgery predict neurological sequelae.

Acknowledgement

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