Inclusion of Mechanical Ventilation in Severity Staging of Tuberculous Meningitis Improves Outcome Prediction

Jayantee Kalita,^{1*} Usha K. Misra,¹ Varun K. Singh,² Prakash C. Pandey,¹ and Justin Thomas¹

¹Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; ²Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Abstract. Patients with tuberculous meningitis (TBM) in any stage of the British Medical Research Council (BMRC) scale, if requiring mechanical ventilation (MV), are likely to have a poor outcome. We report the usefulness of BMRC, BMRC-MV, and BMRC-hydrocephalus (BMRC-HC) staging, and Haydarpasa Meningitis Severity Index (HAMSI) scoring in predicting the outcome of TBM. One hundred ninety-seven TBM patients were analyzed from a prospectively maintained TBM registry. The severity of meningitis was categorized using BMRC (stages I–III), BMRC-MV (I–IV [MV patients were grouped as stage IV]), and BMRC-HC (I–IV [BMRC stage III patients with hydrocephalus were grouped as stage IV]). Haydarpasa Meningitis Severity Index scoring was categorized as < 6 and ≥ 6 . The outcome was defined at 6 months using the modified Rankin Scale (mRS) as death, poor (mRS score > 2), or good (mRS score ≤ 2). Forty-nine (25%) patients died. BMRC-mechanical ventilation stage IV had the highest predictive value for defining death, with a sensitivity of 88% and a specificity of 86%. About 81.7% of surviving patients had a good outcome at 6 months. BMRC-mechanical ventilation stages I–III had the highest predictive value for defining good outcome, with a sensitivity of 93% and a specificity of 61%. In TBM, BMRC-MV staging has the best predictive value for defining death and disability.

INTRODUCTION

Tuberculosis is a major health problem in the developing countries. The annual incidence of tuberculosis in the developing countries is 110–165 cases/100,000 and that in the United States is 9/100,000 population.¹ Central nervous system (CNS) tuberculosis results in 20–30% deaths, and up to 50% survivors have severe neurological sequelae.^{2–7} Tuberculous meningitis (TBM) has diverse clinical manifestations ranging from a mild illness to deep coma. Defining disease severity is important for treatment strategies and predicting outcome. The severity of TBM was defined in 1948 by the British Medical Research Council (BMRC) into stages I, II, and III based on meningitis symptoms, focal neurological deficit, and level of consciousness.⁸ In the earlier studies, the outcome of TBM was related to the stage of meningitis, but in the post-computerized tomography (CT) scan and magnetic resonance imaging (MRI) era, many studies did not find the relationship of BMRC with outcome.^{9–11} The discovery of CT scan and MRI has helped in understanding the structural brain changes in TBM, and these imaging techniques are greatly useful in the diagnosis and management. Hydrocephalus is although a correctable complication of TBM, but it predicts a poor outcome.^{12–14} Similarly, infarction is also a poor prognostic predictor of TBM.¹⁵ A study on TBM has reported better predictive value of the Haydarpasa Meningitis Severity Index (HAMSI) scoring system including clinical, radiological, and comorbidities than the BMRC scale.¹³ The development of neurocritical care provided opportunity to treat seriously ill TBM patients, who otherwise might have died. In a study, TBM patients requiring mechanical ventilation (MV) had a higher mortality (73%) than those who did not require MV (1.1%).¹⁶ Similar results have also been reported by others.^{12,17} It may be appropriate to stage the patients requiring MV to a separate stage, which may have a better predictive value.

Similarly, categorizing the patients in the BMRC stage III with hydrocephalus to a different group may also improve the predictive value. In this study, we compare the relative usefulness of BMRC, BMRC-mechanical ventilation (BMRC-MV), BMRC-hydrocephalus (BMRC-HC), and HAMSI scoring in predicting death and disability of the patients with TBM.

Subjects and methods. This study was conducted in a tertiary care teaching hospital in India. The patients with TBM admitted during January 2014–December 2018 were included from a prospectively maintained TBM registry, which was approved by the Institute Ethics Committee (2013-83-EMP-72; 2018/165PGI-BE).

Inclusion criteria. The diagnosis of TBM was based on clinical, cerebrospinal fluid (CSF), and CT/MRI criteria.⁵

1. Essential criteria: This group included patients with fever, headache, and/or vomiting for more than 5 days in whom malaria, septic, and fungal meningitis were excluded.
2. Supportive criteria:
 - a. Cerebrospinal fluid cells 10–500/mm³ ($> 50\%$ lymphocytes), protein > 1 gm/l, and negative culture for pyrogenic bacteria and fungi;
 - b. Cranial CT or MRI evidences of exudates, hydrocephalus, infarction, or tuberculoma in isolation or various combinations; and
 - c. Evidence of extra CNS tuberculosis.
3. Exclusion of alternative diagnosis.

Exclusion criteria. The patients with organ transplantation, malignancy, pregnancy, preexisting CNS disease, immune-mediated disease, preexisting liver disease, and kidney failure and those on immunosuppressant or chemotherapy were excluded.

Clinical evaluation. A detailed clinical history including demographic information and comorbidities was noted. The level of consciousness was assessed by the Glasgow Coma Scale (GCS). The presence of papilledema, cranial nerve palsy, muscle weakness, and abnormality in tone and tendon reflexes was noted. Sensations and coordination were tested in conscious cooperative patients.

* Address correspondence to Jayantee Kalita, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014, India. E-mails: jayanteek@yahoo.com or jkalita@spgpi.ac.in

Investigations. Complete hemogram, serum chemistry, chest radiograph, ultrasound abdomen, and electrocardiography were performed. Cerebrospinal fluid was analyzed for cells, protein, and glucose. Cerebrospinal fluid was also subjected to smear and culture for *Mycobacterium tuberculosis* and pyogenic bacteria. Polymerase chain reaction (PCR) for *M. tuberculosis* and enzyme-linked immunosorbent assay for cryptococcal antigen in CSF were also performed.

Cranial imaging. Cranial CT scan was performed using a third-generation CT scanner, and cranial MRI was performed using a 3T MRI scanner (GE medical system, Milwaukee, WI). Axial images were obtained in T1, T2, fluid attenuation inversion recovery (FLAIR), diffusion weighted image (DWI), and T1 contrast. The presence of exudates, hydrocephalus, infarction, and tuberculoma was noted.

Diagnostic categorization of TBM. The patients were diagnosed as definite TBM if acid-fast bacillus was demonstrated in smear or culture, or if PCR was positive for *M. tuberculosis*. In the absence of bacterial confirmation, patients with essential and two supportive criteria were categorized as probable TBM and essential with one supportive criterion as possible TBM.⁴

Severity staging of TBM. The patients were categorized using the following staging criteria:

British Medical Research Council staging. Stage I = meningitis only, stage II = meningitis with lethargy or cranial nerve palsy, and stage III = meningitis with stupor, gross paralysis, or paresis.⁸ In stage III, we considered GCS score < 11, and for stage II GCS scores 11–14 for quantification of altered sensorium.

British Medical Research Council-mechanical ventilation staging. Stages I–III as before. Any patient in stage I, II, or III requiring MV was categorized as stage IV.

British Medical Research Council-hydrocephalus staging. Stages I–III as before. Patients in stage III having hydrocephalus on CT or MRI were categorized as stage IV.

Haydarpasa Meningitis Severity Index scoring. It is a composite scoring in which altered sensorium weighted as 3, altered sensorium with nausea and vomiting 1, diabetes mellitus 3, immunosuppression 2, neurological deficit 1, hydrocephalus 1, and vasculitis 1.¹³ We have considered vasculitis if there was infarction on MRI.

The BMRC staging was performed at admission, and the others were performed at the worst clinical and/or radiological condition during the hospital stay.

Treatment. All the patients received standard four-drug antitubercular treatment (isoniazide 5 mg/kg to 300 mg, rifampicin 10 mg/kg to 450 mg, ethambutol 15 mg/kg to 800 mg, and pyrazinamide 25 mg/kg to 1,500 mg daily).¹⁸ Some patients also received levofloxacin 500 mg daily. All the patients received prednisolone 40 mg daily for 1 month, which was then tapered in the next month. Aspirin 150 mg was also prescribed to all. The patients with seizure received levetiracetam, clobazam, or lacosamide, and those with hydrocephalus with deteriorating consciousness were treated with ventriculoperitoneal shunt surgery. The patients with respiratory failure evidenced by acidosis (pH < 7.3), hypercarbia (PaCO₂ > 50 mm of Hg), or hypoxemia (PaO₂ < 60 mm of Hg) in arterial blood gas analysis (ABG) were intubated and mechanically ventilated.¹⁶ They were monitored in the intensive care unit (ICU) and ABG, blood counts, and blood or body fluid cultures were performed as and when needed. All

the patients received supportive care including fluid, electrolyte, calorie, and nursing care.

Outcome. The patients were followed up for 6 months. Day of death and good outcome from the initiation of treatment was noted. At 6 months, the outcome was assessed by the modified Rankin Scale (mRS),¹⁹ and was categorized as good (mRS ≤ 2) or poor (mRS > 2).²⁰

Statistical analysis. Death and poor outcome were compared among BMRC, BMRC-MV, BMRC-HC staging, and HAMSI scoring. Sensitivity, specificity, positive predictive value, and negative predictive value in predicting death and poor outcome at 6 months of three different staging systems were evaluated. Kaplan–Meier analysis was performed for cumulative survival using BMRC, BMRC-MV, BMRC-HC staging, and HAMSI scoring system. A similar statistical analysis was also performed for poor outcome. Univariate regression analysis was performed for death and poor outcome using clinical, laboratory, and MRI findings followed by multivariate analysis with Bonferroni correction. A hazard ratio of various stagings in predicting death and poor outcome was also evaluated using Cox regression analysis. A corresponding “test statistic” having a two-tailed *P*-value of < 0.05 was considered significant. The statistical analysis was performed using SPSS 20 version (Chicago, IL).

RESULTS

One-hundred and ninety-seven patients with TBM were included. The median age was 30 (range 3–75) years, 103 (52%) of whom were males. Sixty (30%) patients had definite TBM, and the remaining 137 (70%) had probable TBM. Cranial MRI was abnormal in 177 (90%) patients and included exudates in 100 (51%), hydrocephalus in 89 (45%), tuberculoma in 115 (58%), and infarctions in 76 (39%) patients. The clinical and radiological details are presented in Supplemental Table 1. The proportions of patients in four staging scales are summarized in Table 1. Three patients from BMRC stage I and 30 patients each from BMRC stages II and III required MV

TABLE 1

Proportion of tuberculous meningitis patients in different severity staging scales

BMRC staging, <i>n</i> (%)	
I	39 (20)
II	94 (48)
III	64 (32)
BMRC-mechanical ventilation staging, <i>n</i> (%)	
I	36 (18)
I	64 (32)
III	34 (17)
IV	63 (32)
BMRC-hydrocephalus staging, <i>n</i> (%)	
I	39 (20)
II	94 (48)
III	31 (16)
IV	33 (16)
Haydarpasa Meningitis Severity Index score, <i>n</i> (%)	
≤ 1	42 (21)
2	25 (13)
3	29 (15)
4	43 (22)
5	33 (16)
≥ 6	25 (13)

BMRC = British Medical Research Council.

during the hospital stay, and hence these patients were categorized as stage IV in the BMRC-MV staging. Thirty-three patients from BMRC stage III developed hydrocephalous and were categorized as BMRC-HC stage IV.

Association of death with various severity staging scales. Forty-nine (25%) patients died; 21 (43%) within 1 month, 24 (49%) during 1–3 months, and four (8%) during 3–6 months of antitubercular treatment. The proportions of deaths in BMRC stage II (24/49, 49%) and stage III (20/49, 41%) were higher than those of deaths in stage I (5/49, 10%). In BMRC-MV staging, 43 (88%) deaths occurred in stage IV patients. In BMRC-HC staging, eight (16%) patients died in stage IV. The occurrence of death was not proportional to the HAMSI score. BMRC-mechanical ventilation stage IV had the highest predictive value for death, with a sensitivity of 88% and a specificity of 86% followed by BMRC stage III, 41% and 70%, respectively (Supplemental Table 2, Table 2). On the Kaplan–Meier survival analysis, there was no difference in the survival times of the patients in stages I, II, and III of the BMRC staging ($P = 0.11$). On the BMRC-MV scale, there was a significant difference in the proportion of patients in stages I, II, III, and IV. The log-rank test showed a significant difference in the survival time between stage IV and other three stages ($P < 0.001$); but there was no difference between stages I–III. The BMRC-HC scale did not show a significant difference between the stages ($P = 0.09$). In the HAMSI scoring, we had observed a higher probability of survival in the patients who scored 6 or more ($P = 0.009$; Figure 1).

Functional outcome at 6 months. At 6 months, 121/148 patients (81.7%) had a good outcome. The predictive value of good outcome in the surviving patients was the highest in the BMRC-MV staging, with a sensitivity of 93% and specificity of 61% in stages I, II, and III patients. The sensitivity of BMRC stages I and II in predicting a good outcome was 75%, with a specificity of 41%. The BMRC-HC staging had a higher sensitivity with a lower specificity. The details are presented in Table 3 and Supplemental Table 2. On the Kaplan–Meier analysis, stage IV of the BMRC-MV scale had the least probability of a good outcome compared with stages I–III. On the BMRC scale, there was also a trend of worse outcome with increasing severity. The increasing severity of meningitis in the BMRC-HC and HAMSI score did not follow any trend (Figure 2). On univariate analysis, BMRC stage III ($P = 0.01$), BMRC-MV stage IV ($P < 0.001$), BMRC-HC stage IV ($P < 0.02$), HAMSI score ($P = 0.003$), status epilepticus ($P = 0.007$), and duration of illness ($P = 0.02$) were associated with poor outcome. On Cox regression analysis, poor outcome was also less frequent in BMRC-MV stage I (adjusted hazard ratio [AHR] 0.039; 95% CI 0.004–0.39; $P = 0.006$), stage II (AHR 0.161; 95% CI 0.075–0.347; $P < 0.001$), and stage III (AHR 0.215; 95% CI 0.086–0.541; $P = 0.001$) than in stage IV. The BMRC-HC did not follow any trend.

Predictors of death and disability using baseline parameters including BMRC. At admission, 39 (20%) patients were in stage I, 94 (48%) in stage II, and 64 (32%) in stage III on

TABLE 2
Relationship of various clinical and radiological variables with death in patients with tuberculous meningitis

	Survived ($n = 148$)	Death ($n = 49$)	P -value
Age (years)	32.95 $\pm$ 15.95	32.06 $\pm$ 12.06	0.72
Gender (female), n (%)	71 (48)	23 (47)	0.90
Duration of illness (days)	60 (5–210)	60 (7–240)	0.19
Glasgow Coma Scale score	12.20 $\pm$ 2.95	10.84 $\pm$ 3.46	0.01
Cranial nerve palsy, n (%)	58 (39)	13 (26)	0.11
Focal motor deficit, n (%)	87 (59)	29 (59)	0.96
Seizure, n (%)	63 (42)	34 (69)	0.001
Magnetic resonance imaging, n (%)			
Exudate	76 (51)	24 (49)	0.77
Hydrocephalus	67 (45)	22 (45)	0.96
Infarction	59 (40)	17 (35)	0.52
Tuberculoma	90 (61)	25 (51)	0.23
BMRC staging, n (%)			0.11
I	34 (23)	5 (10)	
II	70 (47)	24 (49)	
III	44 (30)	20 (41)	
BMRC-mechanical ventilation staging, n (%)			< 0.001
I	34 (28)	2 (4)	
II	61 (41)	3 (6)	
III	33 (22)	1 (2)	
IV (any stage + MV)	20 (13.5)	43 (88)	
BMRC-hydrocephalus staging, n (%)			0.10
I	34 (23)	5 (10)	
II	70 (47)	24 (49)	
III	19 (13)	12 (25)	
IV (stage III + HC)	25 (17)	8 (16)	
Haydarpasa Meningitis Severity Index score, n (%)			0.01
≤ 1	37 (25)	5 (10)	
2	14 (9)	11 (22)	
3	22 (15)	7 (14)	
4	31 (21)	12 (25)	
5	21 (14)	12 (25)	
≥ 6	23 (16)	2 (4)	

BMRC = British Medical Research Council.

FIGURE 1. Kaplan-Meier survival curves show cumulative survival probability in (A) British Medical Research Council (BMRC) scale, (B) BMRC-mechanical ventilation (BMRC-MV) scale, (C) BMRC-hydrocephalus scale, and (D) Haydarpasa Meningitis Severity Index (HAMSI) score. The log-rank test shows that there is no difference in the survival time of the patients between three stages of BMRC ($P = 0.11$) and four stages of BMRC-HC ($P = 0.09$). There is a significant difference in survival time between stage IV and other three stages of BMRC-MV ($P < 0.001$), but for the rest of the pairs, it is statistically insignificant. The difference is also significant in the survival time among the patients with different HAMSI scores ($P = 0.009$), but there is no increase of deaths with rise in score. The chart above the graphs shows the number of individuals at risk.

the BMRC staging. On univariate analysis, survival at 6 months was related to GCS score ($P = 0.007$) and seizure ($P = 0.002$). On Cox regression analysis also, the independent predictors of 6-month survival were GCS score (AHR 0.91; 95% CI 0.84–0.99; $P = 0.03$) and seizure (AHR 2.38; 95% CI 1.28–4.40; $P = 0.006$).

Outcome predictors in mechanically ventilated patients.

Sixty-three patients needed MV, of whom 43 (68.2%) died and 12 (19%) only had a good outcome. The clinical features, MRI findings, and comorbidities in the patients who died or had poor recovery were similar to those who survived or had a good outcome (Supplemental Tables 3 and 4).

DISCUSSION

In the present study, the BMRC-MV staging in TBM had the highest predictive value for defining death and disability at 6 months compared with the BMRC staging. The BMRC-HC staging and the HAMSI scoring did not have a linear

relationship with death and functional outcome. The need of MV in any disease suggests more severe illness with higher mortality.^{21–23} Patients with septicemia, H1N1, dengue and scrub typhus on the MV have fewer deaths and good functional outcomes unlike TBM.^{21,24,25} In a study on 164 patients with acute encephalitis syndrome (AES), 69 (42%) needed MV. Forty-three (26%) patients died, and all were in the MV group. Higher Sequential Organ Failure Assessment score and untreatable etiology were independent predictors of death. However, at 3 months, 14% of patients had poor outcome. In this study, the etiologies of AES patients were viral in 44 (27%), scrub typhus in 48 (29%), malaria in six (4%), and unknown in 56 (34%).²¹ In a retrospective study on 103 patients with encephalitis illness of various etiology (viral in 27.2%, bacterial and fungal in 9.7%, autoimmune in 16.5%, and undetermined in 46.6%), about 95% of mechanically ventilated patients died.²² In another retrospective study including 198 patients with AES, MV, age ≥ 65 years, immunocompromised states, thrombocytopenia, and CSF polymorphonuclear pleocytosis

TABLE 3

Relationship of various clinical and radiological variables with functional outcome at 6 months in the surviving patients with tuberculous meningitis

	Good (n = 121)	Poor (n = 27)	P-value
Age (years)	32.84 ± 16.2	33.4 ± 15	0.86
Gender (female), n (%)	60 (49.5)	11 (41)	0.40
Duration of illness (days)	66.92 ± 59.07	92.25 ± 57.89	0.045
Glasgow Coma Scale score	12.5 ± 2.9	10.8 ± 2.9	0.007
Cranial nerve palsy, n (%)	43 (35)	15 (56)	0.054
Focal motor deficit, n (%)	65 (54)	22 (81)	0.008
Seizure, n (%)	48 (40)	15 (56)	0.13
Status epilepticus, n (%)	5/48 (10)	5/15 (33)	0.049
Magnetic resonance imaging, n (%)			
Exudate	58 (48)	18 (67)	0.08
Hydrocephalus	49 (40)	18 (67)	0.01
Infarction	44 (36)	15 (56)	0.06
Tuberculoma	70 (58)	20 (74)	0.12
BMRC staging, n (%)			0.006
I	34 (28)	0	
II	52 (43)	18 (67)	
III	35 (29)	9 (33)	
BMRC-mechanical ventilation staging, n (%)			0.001
II	34 (28)	0	
III	48 (40)	13 (48)	
IV (any stage + MV)	27 (22)	6 (22)	
BMRC-hydrocephalus staging, n (%)			0.003
I	12 (10)	8 (30)	
II	34 (28)	0	
III	52 (43)	18 (67)	
IV (stage III + HC)	15 (12)	4 (15)	
IV (stage III + HC)	20 (17)	5 (18.5)	
Haydarpasa Meningitis Severity Index			0.002
Severity score, n (%)			
≤ 1	36 (30)	1 (3.7)	
2	13 (11)	1 (3.7)	
3	19 (15)	3 (11)	
4	24 (20)	7 (26)	
5	12 (10)	9 (33)	
≥ 6	17 (14)	6 (22)	

BMRC = British Medical Research Council.

were associated with poor prognosis.²³ Another study compared death and functional outcome in 38 MV and 36 non-MV patients with TBM. About 71% of MV patients died, and the remaining patients had poor outcome at 3 months, whereas none in the non-MV group died, and only 11% patients had a poor outcome.¹⁶ This study raised the possibility of grouping the MV patients of any BMRC stage to a separate stage.

Various staging scales have been described to define the severity of TBM to predict death and disability.^{8,9,13} BMRC staging is mainly used in most of the studies and has been reported as a robust predictor of short- and long-term outcomes.^{8,26–31} However, in the era of intensive care facilities, many authors did not find the BMRC staging as a prognostic predictor.^{9,13,32} In the initial BMRC staging, altered sensorium was measured subjectively as the GCS score was developed in 1974.³³ Since then, the GCS score has been an independent predictor of outcome.^{34–38} Therefore, we have used the GCS score for defining various grades of altered sensorium in BMRC staging. The BMRC staging was able to define patients with good outcomes at 6 months between stages I–III meningitis, but there was no difference in deaths among the three groups. Using the BMRC-MV staging, patients in stage IV stratified the highest deaths and the worst outcome compared with the patients in stages I–III, but there was no difference between the stages I–III. In a study on 43

TBM patients, the Acute Physiology and Chronic Health Evaluation II and the GCS score were more sensitive than the BMRC staging in predicting the death and disability.⁹ In our study, there was no linear correlation of the HAMSII score with death and disability. This may be because of the less number of patients with immunosuppression and diabetes in our cohort.

The higher proportion of deaths in TBM patients needing MV in our study is unlikely because of the quality of ICU care because mortality in Guillain-Barre syndrome and myasthenic crisis in our ICU are comparable to the developed countries.^{39–41} Higher deaths in the TBM patients compared with dengue, scrub typhus, and Japanese encephalitis may be due to the difference in underlying disease pathophysiology. Dengue and Japanese encephalitis are monophasic illness; once the acute crisis is over, the patients start improving. Similarly, cerebral malaria and scrub typhus respond to the specific treatment. Although tuberculous meningitis is a treatable disease, it requires longer duration of treatment and about 40–60% may deteriorate on antitubercular treatment because of paradoxical response.⁴²

Limitation. This is a retrospective study, although the data were obtained from a prospectively maintained registry. Ours is a referral center, and more severe meningitis dominated the study cohort. The application of this BMRC-MV in the non-ICU setting may be extrapolated to any BMRC patients with respiratory failure based on clinical and ABG parameters.

FIGURE 2. Kaplan-Meier survival curves show difference in good outcome during 6 months of follow-up in the patients with tuberculous meningitis in (A) British Medical Research Council (BMRC) scale, (B) BMRC-mechanical ventilation (BMRC-MV) scale, (C) BMRC-hydrocephalus scale, and Haydarpasa Meningitis Severity Index (HAMSI) score of ≤ 1 , 2, 3, 4, 5, and ≥ 6 (D). The log-rank test shows that there is a significant difference in the probability of good outcomes among three stages of BMRC ($P = 0.003$), and between stage IV and other three stages of BMRC-MV ($P < 0.001$). The log-rank test also shows that the difference in the probabilities of good outcome among the different stages of BMRC-HC is significant, except in stages II and IV ($P = 0.005$). However there is no inverse relationship of good outcome with the HAMSI score. The chart below the graphs shows the number of individuals at risk. The patients with poor outcome group also included death in the analysis.

Conclusion. The BMRC-MV staging in TBM has the best predictive value in defining death and functional outcome at 6 months. Future studies in TBM are desirable, aiming at deriving necessary treatment strategies in MV patients.

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Authors' addresses: Jayantee Kalita, Usha K. Misra, Prakash C. Pandey, and Justin Thomas, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India, E-mails:

jayanteek@yahoo.com, drukmisra@rediffmail.com, drprakashpandey@gmail.com, and dr.justinthomas@gmail.com. Varun K. Singh, Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, E-mail: mailurvarun@gmail.com.

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