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Seizures in multiple sclerosis in Eastern India

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Abstract

Multiple Sclerosis (MS) is a disease of white matter and seizure is the resultant effect of gray matter pathology and hence is usually infrequent. The aim of this study was to evaluate the frequency and clinical characteristics of seizures in MS patients seen at a tertiary care neurological institute in Eastern India. In a series of 70 consecutive clinically definite MS patients seen over a period of 14 years, there were 12 patients with seizures. Seven patients (10%) had seizures after the onset of MS symptoms. Out of these 7 patients, the mean age of onset of MS symptom was 24.5 years, and that of seizure was 27 years. The male to female ratio was 1: 2.5. The first seizure occurred during acute MS relapse in 5 patients. Two patients developed seizures after IV methylprednisolone. The remaining 5 patients manifested partial seizure clinically with or without secondary generalization. Four patients had abnormal EEG, and 6 had gray matter lesions in MRI brain.
In *conclusion*, there was increased frequency of seizure of commonly focal variety among MS patients as compared to general population.

INTRODUCTION

Seizure disorder is considered uncommon in multiple sclerosis (MS), since it is a white matter disease. However seizure has been documented as commoner in MS patients as compared to general population.[1] The prevalence of seizure in various community studies from India varies from 2.47 per 1000 to 8.83 per 1,000 populations[2-6] and the mean overall prevalence is about 6 per 1000. The frequency of seizure in MS in different Indian studies varies from 3.9 to 9%[7-10] (Table 1) and 1.9 to 7.5% from Western countries.[11-14] Various explanations for seizures in MS have been offered. These are: plaques of demyelination affecting the cortical or sub-cortical areas, electrolyte changes in the plaque, reactive gliosis, edema, and impaired Na^+K^+ATP-ase enzyme activity.[1] There is no study on the clinical pattern, EEG and MRI correlation and therapeutic response of seizures in MS from India. This is a study to determine the clinical and electrophysiological profile of seizures among patients suffering from MS as observed in a tertiary care neurological institution from Eastern India.

Table 1: Frequency of seizure in MS in previous studies

Authors	Year of publication	Place of study	Sample size (no of patients)	Frequency of seizures
Syal *et al*[7]	1999	India	100	4%
Bhatia *et al*[8]	1996	India	50	6%
Chopra *et al*[9]	1980	India	54	9%
Singhal *et al*[10]	1987	India	127	3.9%
Ghezzi *et al*[13]	1990	Milan	2,553*	2.33%
Sokic *et al*[14]	2001	Belgrade	268	7.5%
Kinnuen and Wikstrom[11]	1986	Helsinki	599	3.5%
Olafsson E *et al*[12]	1999	Iceland	188	1.9%

*Of those with probable MS, 40 out of 2,553 patients had seizures (1.6%). Of those with definite MS, 2.33% had seizures

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METHODS

This is a retrospective study based on the review of the patients's chart. The study patients were from the 70 consecutive cases of clinically definite MS, admitted or attended the outpatient department over the last 14 years at Bangur Institute of Neurology and Institute of Post Graduate Medical Education and Research, Kolkata, India. The diagnosis of MS was according to the criteria by Poser *et al*.[15] The inclusion criterion was occurrence of seizure after onset of MS symptoms. The patients whose seizures preceded the clinical manifestations of MS were noted, but excluded from the main analysis. The seizure was classified according to the International League against Epilepsy classification.[16] EEG, MRI of brain with contrast whenever possible, CSF and evoked potential studies were performed in all patients.

RESULTS

Out of a total of 70 patients who were identified to have clinically definite MS in the study period, 12 patients (17%) had seizures. Five patients had seizures preceding the onset of MS symptom. Of these, 3 patients had inactive epilepsy with onset at childhood. None of these patients reported seizure recurrence with onset of MS symptoms. Two other patients had active epilepsy and were on antiepileptic drugs. Of these two patients, the latency between the onset of seizure and that of first MS symptom was about 5 years. Both patients reported an increase in seizure frequency after onset of MS symptoms requiring increased dose of antiepileptic drugs. In most of the cases, the seizures were not temporarily associated with onset of MS symptom. The exacerbation of seizures was unrelated to steroid medication. There was also no aggravation of MS symptoms with the seizures or immediately following the ictus.

There were thus 7 patients (10%) who developed seizure after onset of MS symptoms. The men to women ratio were 1: 2.5. The mean age of onset of first symptom of MS was 24.5 years and that of onset of seizure was 27 years, ranging between 21 to 37 years. The mean duration of follow up since the onset of seizure was 4 years. The clinical manifestations of MS and seizure manifestations are shown in Table 2. Two patients developed generalized tonic clonic seizures after administration of intravenous methylprednisolone. Two patients had focal motor seizures with secondary generalization. The rest of the 3 patients had complex partial seizure, simple partial seizure and frontal lobe seizure respectively. The frequency of seizure was one to two episodes per year. The first seizure occurred during the acute relapse of MS in 5 out of 7 patients. For the other 2 patients, the first seizure occurred during MS remission. Of the 5 patients whose first seizure was during MS relapse, 2 patients had seizures during administration of IV methylprednisolone. Both the patients did not have any further seizure. The other 3 patients however, had persistent seizures when the MS was in remission. None of the patients had status epilepticus. All the seven patients were treated with antiepileptic drugs, which were either sodium valproate or carbamazepine or both. Whereas the 2 patients with seizures during methylprednisolone were given short course of antiepileptic drugs, the others required multiple drugs given long term to control the seizures.

Table 3 summarizes the EEG, MRI, cerebrospinal fluid oligoclonal band and evoked potentials of the MS patients with seizures. As shown, EEGs were abnormal in 4 patients. Six patients showed gray matter involvement in frontal, temporal or parieto-occipital lobes. The plaques were also seen in the adjacent juxta-cortical region, as well as white matter in periventricular area, brainstem and corpus callosum. Six of the patients fulfilled MRI criteria of MS proposed by Barkhof *et al*[17] and Tintore *et al*.[18] Repeat MRI of brain after seizure in 2 patients showed new plaques.

DISCUSSION

The occurrence of seizures in MS was considered as chance association by Matthews.[19] Recent studies have shown increasing incidence of seizures in MS as compared to general population.[11-14] The seizure may occur in MS as presenting feature, during treatment or following relapse. But it is also equally possible that it may exacerbate underlying seizure disorders as evident from two of our 5 patients who had seizures preceding onset of MS symptoms.

The incidence of seizure in MS in the current study is 10%. This is higher than the prevalence of epilepsy (0.6%) from general population in India.[3] It is also higher than the frequency of seizures in MS previously reported from India and several other countries (Table 1).[11-14] The variation in rate among various MS studies was probably contributed by differences in sample size, ethnicity, geography and varying inclusion criteria.

Being a symptomatic seizure, it is expected that the seizure manifestation should be focal.

Table 2: Clinical features of MS patients with their seizure

Patients	Sex	Age	Clinical manifestations of MS	Clinical sites of involvement of MS	Seizure manifestations
1	M	21	2 attacks, left hemiparesis, hypoesthesia and visual impairment.	Optic nerve, spinal cord	GTCS after injection of methyl prednisolone
2	F	24	2 attacks, darkening of vision right side, dysphagia and unsteadiness of gait.	Optic nerve, brainstem, cerebellum	Complex partial seizures
3	M	32	3 attacks, (L) hemiparesis, gait disturbances, sphincteric incontinence, visual disturbances.	Optic nerve, brainstem, cerebellum, spinal cord	Frontal lobe seizures (adversive seizures)
4	F	37	4 attacks, darkening of vision right side, hemiparesis, electric current like sensation right face and left limbs precipitated by chewing, diplopia, vertigo.	Optic nerve, brainstem, spinal cord	GTCS after injection of methyl prednisolone
5	M	27	2 attacks, visual disturbances, quadriparesis, ataxia, diplopia.	Optic nerve, brainstem, cerebellum, spinal cord	Left focal motor seizures with secondary generalization
6	M	23	2 attacks, visual disturbances, gait ataxia, hemiparesis.	Optic nerve, cerebellum, spinal cord	Left focal seizures with secondary generalization.
7	M	24	Primary progressive, visual disturbances, bladder and bowel incontinence, ataxia, diplopia, left hemiparesis and hypoesthesia.	Optic nerve, brainstem, cerebellum, spinal cord	Simple partial seizures

Age: Age of onset of seizures in years
GTCS: generalized tonic clonic seizures

Except 2 patients whose seizures were precipitated by intravenous methylprednisolone, all the other 5 patients manifested clinically as focal seizures with or without secondary generalization. Three out of 4 patients also showed focal interictal EEG discharges (Table 3). Kinnunen and Wikstrom[11] also reported predominantly partial seizures in their patients.

Due to its ability to demonstrate subclinical brain lesions, MRI brain is used to improve the sensitivity of MS diagnosis, as well as to assess disease activity and treatment efficacy. Six of our patients showed gray matter involvement adjacent to the white matter, in the frontal, temporal, and parieto-occipital lobes. Russco *et al*[20] reported T_2 shortening in both cortical gray matter and subcortical white matter in patients with cognitive dysfunction due to non-haeme iron deposition. It is possible that seizure in a patient with severe MS may be due to similar gray matter changes. Repeat MRI of brain after seizure could be done in 2 of our patients showing new plaques. Similarly Thompson *et al* have demonstrated new or enhancing lesion MRI lesions in gray and subcortical area among MS patients with seizures.[21] It is possible that the occurrence of

Table 3: Investigations of MS patients with seizures

Investigations		No. of patients abnormal (n = 7)	Percent abnormal
EEG			
Generalized discharges Focal with secondary generalized discharge	1 3	4	57
MRI of brain showing evidence of gray matter involvement			
Frontal lobe plaque Parieto-occipital lobe plaque Temporal lobe plaque	2 2 2	6	86
Cerebrospinal fluid: presence of oligoclonal band		2	29
Visual evoked potential		7	100
Brainstem auditory evoked potential		2	29
Tibial nerve somatosensory evoked potential		3	43

seizures following MS symptoms may be due to new lesions.

Seizure in MS may be related to causes other than the underlying disease process. Two of our patients developed generalized tonic clonic seizures just after administration of intravenous methylprednisolone. Intravenous methylprednisolone is known to reduce seizure threshold[22] and thus may induce seizure in a subject who was already prone to convulsive attack because of strategic location of the MS lesions in or close to the gray matter.

In conclusion, we have shown that the frequency of seizure in MS patients is higher than the mean prevalence of epilepsy in the community. MS can aggravate seizure in patients with existing active epilepsy. Methylprednisolone is able to precipitate seizures during treatment of MS relapse. The continuing recurrent seizures are usually focal and probably reflect underlying gray matter involvement. The result of this study from Eastern India is similar to that from the West

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