

Brief Report

Epileptic Seizures in Early-onset Multiple Sclerosis

Masoud Etemadifar MD^{1,2}, Seyed-Hossein Abtahi MD^{1,2}, Nasim Tabrizi MD^{1,2}**Abstract**

Early-onset multiple sclerosis (EOMS) is defined as the first presentation of symptoms in childhood (before the age of 16 years). EOMS occurs in about 0.4% to 10.5% of multiple sclerosis (MS) patients.

In this retrospective population-based study we aimed to describe the clinical/paraclinical details and frequency of epileptic seizures in Iranian EOMS patients registered with the Isfahan Multiple Sclerosis Society (IMSS) from April 2003 to July 2010. EOMS cases were extracted from the Isfahan total MS cohort and included 3522 patients.

A total of 117 EOMS patients (19 males and 98 females) with a mean age at onset of 14.2 ± 2.0 years (range: 7–16 years) were extracted from our database (3.3% of the total cohort). Of cases, ten (one male and nine females) had experienced at least two epileptic seizures, providing a crude prevalence of 8.5%. The frequency of epilepsy in EOMS patients (8.5%, 10/117) was significantly greater ($P < 0.001$) than that of non-EOMS cohort (2.0%, 71/3405). Epileptic seizures occurred before MS onset in two patients, after MS onset in seven, and at MS onset in one as the presenting symptom of the disease.

Our findings mostly indicate an excessive prevalence of epileptic seizures in Iranian EOMS patients (8.5%), which is higher than any other report concerning seizures or epileptic seizures in a large MS series.

Keywords: Early-onset multiple sclerosis, epileptic seizure, frequency, Isfahan, Iran

Cite the article as: Etemadifar M, Abtahi SH, Tabrizi N. Epileptic Seizures in Early-onset Multiple Sclerosis. *Arch Iran Med.* 2012; **15(6)**: 381 – 383.

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the central nervous system (CNS) of unknown origin that generally involves young adults between the age of 20 and 40 years.¹ Early-onset MS (EOMS) is defined as the first presentation of symptoms in childhood (before the age of 16) and is divided into the “true childhood-onset MS” (under the age of 10 years) and “juvenile-onset MS” (between the ages of 10 and 16 years). Juvenile-onset MS is much more common. EOMS occurs in about 0.4% to 10.5% of all MS patients and when compared to adult-onset MS (AOMS), has an acute presentation and leads to rapid hospitalization. EOMS usually represents a complex picture of headache, fever, vomiting, unconsciousness, and noticeable cerebellar or brainstem deteriorations.^{1,2} In the past decade, several small size studies have reported the occurrence of seizures in EOMS cases with various frequencies.^{3–5}

Indeed, since early descriptions, seizures have been recognized as a component of MS. The higher frequency of epilepsy in MS patients in comparison to the general population is a well-demonstrated finding.^{6–8} Several studies have reported the prevalence of epileptic seizures in MS patients with controversial results (0.5% to 8.3%).^{6,7} In a recent review article, the overall prevalence of sei-

zures in the MS population was estimated about 2.2% (CI 95%: 2.0%–2.4%).⁷ Nevertheless, there have been very few studies on the characteristics of epileptic seizures in relatively large EOMS populations. This report looks at the characteristics of epileptic seizures in MS patients who are residents of the province of Isfahan, Iran.

Patients and Methods

This population-based study was performed in Isfahan, a large province (107 003 km²) located in the center of Iran, between latitudes 30 and 34 degrees north of the equator and longitude 49–55 degrees east. According to the 2006 national census, Isfahan has a population of 4,559,256, with similar socio-economic structure and population characteristics compared to the remainder of Iran.⁹

The study was carried out retrospectively; we analyzed the clinical records of MS patients who were registered with the Isfahan MS Society (IMSS) as the only referral center in Isfahan, from April 2003 to July 2010. Overall, 3522 definite MS patients (2716 women and 806 men) were registered with IMSS. They were presumed to be the total cohort of MS patients in Isfahan. The demographic details of this population were described in a recent study.⁹ The diagnosis of MS in this center is based on McDonald criteria that is applicable for both EOMS and AOMS.¹⁰

We inspected IMSS computerized database for cases that had experienced seizures before the age of 16 years. Clinical and demographic data including disease pattern [relapsing-remitting (RR), primary progressive (PP) and secondary progressive (SP)], relapse history (date, duration and type), therapeutic protocols, and Expanded Disability Status Scale (EDSS) were determined based on follow up records.^{1,2,10} Only patients who had two or more seizure

Authors' affiliations: ¹Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran, ²Isfahan Medical Students Research Center (IMSRC), Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding author and reprints: Seyed-Hossein Abtahi MD, S.H.A. Research Center of Neurological-Ophthalmological Sciences (SHARNOS Co.), No. 9, Boroomand St., Seyed-Alikhan, Chaharbagh Abbasi St., Isfahan 81448-14581, Iran.

Tel: +98-913-409-8036, Fax: +98-311-264-3588, E-mail: shf.Abtahi@yahoo.com

Accepted for publication: 14 December 2011

Table 1. Clinical/paraclinical features of 10 early-onset multiple sclerosis (EOMS) patients with epileptic seizures.

Case	1	2	3	4	5	6	7	8	9	10
Sex	F	F	F	M	F	F	F	F	F	F
Age at onset of MS	8	14	15	16	10	14	16	14	12	13
Age at onset of seizure	8	16	15	15	16	15	12	15	15	16
Seizure occurred before/at/after MS onset	After	After	At	Before	After	After	Before	After	After	After
Classification of EOMS	Childhood-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset	Juvenile-onset
Follow-up (year)	7	6	6	10	8	10	6	8	8	9
MS pattern	RR	RR	RR	RR	RR	SP	RR	SP	RR	RR
EDSS at first seizure episode	1	1	1.5	NA	2	2	NA	1.5	1.5	1.5
Final EDSS	3	1.5	2	1.5	1.5	6	2	6	1.5	2.5
Type of seizure	P-GTCS	P-GTCS	P-GTCS	P-GTCS	P-GTCS	P-GTCS	P-GTCS	S-GTCS	P-GTCS	P-GTCS
Number of seizures episodes	>10	2	3	6	2	>10	7	>10	4	5
EEG	Generalized-SW	Right-FL-Spike	Generalized SW	Generalized SW	Left-FL-Spike	Generalized SW	Bifrontal SW	Generalized SW	NL	Generalized SW
Brain MRI at the diagnosis	C, SC, CSO, CC, BS	PV, C, SC,	PV, C, SC	PV, C, SC	PV, C, SC	PV, C, SC	PV, C, SC, CSO	PV, C, SC	PV, C, SC, BS	PV, C, SC
Interferon prescription	Pos	Pos	Pos	Neg	Pos	Neg	Pos	Pos	Pos	Pos
AED	CBZ, VPA, LMT	CBZ	VPA	CBZ	CBZ	CBZ, VPA	VPA	CBZ, VPA, LMT	CBZ	CBZ

MS = Multiple sclerosis, EOMS = early-onset multiple sclerosis, EDSS = expanded disability status scale, RR = relapsing-remitting, SP = secondary progressive, MRI = magnetic resonance imaging, EEG = electroencephalogram, AED = antiepileptic drug, M = male, F = female, P/S-GTCS = primary/secondary-generalized tonic-clonic seizure, SW: spike wave, FL = frontal lobe, PV = peri ventricular, C = cortical, SC = sub-cortical, CSO = centrum semi-oval, BS = brainstem, Pos = positive, Neg = negative, NL = normal, NA = not applicable, CBZ = carbamazepine, LMT = lamotrigine, VPA = valproic acid.

episodes were enrolled.

Eligible EOMS cases were requested to go to the IMSS for final clinical/paraclinical examinations and to provide informed consent. We also performed final magnetic resonance imaging (MRI) and electroencephalography (EEG) for the recruited cases. Data was then entered into the SPSS version 19.00 for appropriate statistical analysis.

Results

Among 3522 MS patients (2716 females and 806 males),⁹ 117 (3.3%) were EOMS and 3405 (96.7%) were non-EOMS. Out of the 117 EOMS cases, ten (one male and nine females) were epileptic, giving a crude frequency of 8.5%. On the other hand 71 epileptic cases (57 males and 14 females) were detected among non-EOMS patients (2.0%). The frequency of epilepsy in the EOMS group was significantly greater than that of the non-EOMS group (Chi-square= 18.24, $P < 0.0001$).

Among total EOMS patients, five cases had "childhood-onset" (5/117), and the remaining had "juvenile-onset" (112/117). Among ten epileptic EOMS patients, all had "juvenile-onset" except one. Therefore, in respect to the total EOMS cohort, the frequency of epileptic seizures among the "juvenile-onset" patients was 8.0% (9/112) and "childhood-onset" patients was 20% (1/5).

Demographic, clinical, and paraclinical details of our ten epileptic EOMS patients are highlighted in Table 1. In these cases, the mean age at MS onset was 13.2 ± 2.5 years (range: 8–16 years) and the mean age at first epileptic seizure was 14.3 ± 2.4 years (range: 8–16 years). At onset, all ten patients had experienced the RR pat-

tern, although two cases entered the SP phase. Seizures occurred before MS onset in two patients, after MS onset in seven, and at MS onset in one as the presenting symptom. In cases that epileptic seizures occurred before MS onset, further seizure episodes had continued until MS was confirmed and extended into the course of the disease. We could not identify any time relationship between seizures and relapses, as none of our cases experienced any co-occurrence of a routine relapse and a seizure episode.

None of our ten patients had any risk factor for seizures, such as perinatal hypoxia, head trauma, CNS infection, or a positive family history of epilepsy. Epileptic seizures were classified as primary generalized tonic-clonic seizure (GTCS) in all cases except one with secondary GTCS. Eight cases were treated by interferon. However, the occurrence of seizures was not seemingly induced by application of the drug. Seven cases were on antiepileptic monotherapy, and three were on polytherapy.

Discussion

This was the first population-based study that exclusively concentrated on epileptic seizures in EOMS. Since 2002, several studies have reported the occurrence of seizures in small pediatric MS cohorts with diverse results (4.5% to 33%).³⁻⁵ Such small studies have raised the possibility of excessive seizures in EOMS in comparison to AOMS. Renoux et al. have recently shown that encephalitic symptoms, e.g., seizures, occurred more frequently in EOMS (7%) in comparison to AOMS.² In the present study, we showed that epileptic seizures were significantly more frequent among EOMS patients in comparison to non-EOMS cases (8.5%

vs. 2.0%), and this finding provided more support for the related suggestions.

The concurrence of MS and epilepsy is not incidental.⁸ Nevertheless, suggestion of a precise and uniform causal relationship between the two entities seems to be difficult. The impact of cortical plaques in triggering seizures is a well-established hypothesis.⁶⁻⁸ Moreover, the role of subcortical plaques in the seizure activity of patients with MS and epilepsy is considerable in the current literature.⁸ All our cases had cortical and sub-cortical plaques on their brain MRI scans.

To date, notwithstanding the pathophysiologic fact that MS is a multifocal CNS disorder and focal lesions are presumed to trigger focal seizures or secondary GTCS, several studies (at least seven) have reported the predominance of primary GTCS in MS. These examples included hospital- and population-based studies.⁷ Comparatively, the majority of our cases (9/10) had seizures with primary GTCS and one had secondary GTCS.

Treatment can be considered a potential connecting component between MS and seizures. Current medications for MS can be epileptogenic, yet antiepileptic drugs can mimic the symptoms of MS.^{6,7} However, we did not find any evidence supporting this correlation in our EOMS series.

Excluding the cases that presented with seizures before the confirmation of MS, our patients developed seizures during the RR phase and not during the advanced stages. Consequently, our findings indicated that the occurrence of seizures did not correlate with the severity of EOMS. This finding has pointed towards the occurrence of seizures at any stage of MS, and is explainable by the fact that cortical lesions can occur at early stages of MS.⁶⁻⁸ In our series, seizures have been found to be the presenting symptom of EOMS in 10% of cases, which was in accordance with the literature.⁸

From another point of view, our EOMS cases manifested seizure episodes completely separate from their routine MS relapses. This can be explained by the presence of silent plaques making enough cortical irritation to result in seizures but not potent enough to cause a relapse.^{7,8}

Taken together, our findings mostly indicate an excessive prevalence of epileptic seizures in Iranian EOMS patients (8.5%), which is higher than our non-EOMS cases and higher than other reports concerning seizures or epileptic seizures in a large MS series.⁶⁻⁸ When our findings on the "childhood-onset" subgroup of EOMS are considered (1/5, 20%), this excessive prevalence might be even more prominent. In conclusion, these findings when compared

with previous investigations might be supportive of an increased prevalence of epileptic seizures in EOMS. However, more studies are needed to confirm these findings.

Funding source

This study was funded by the SHARNOS Research Center (*Knowledge of Vision and Motion*).

Conflict of interest

Neither the authors nor the funding agency have any proprietary interest in the materials presented herein.

Acknowledgment

This study is dedicated to the memory of Dr. Afsane Khandan (Iranian internist) who devoted her precious life to health development and medical research.

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