Original article

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Seizures as a manifestation of multiple sclerosis

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ABSTRACT – *Background*. The incidence of seizures is generally accepted to be greater in patients with multiple sclerosis (MS) than in the general population, and rarely, MS can initially present as seizure. *Objective*. To present a case report of seizure as the initial symptom of MS, to quantify the occurrence of seizures among MS patients, and to classify patients according to when seizures occur relative to onset of MS. *Methods*. The medical history of patients presenting with MS and seizure in our clinic was examined. In addition, 25 scientific papers were reviewed and the number and characteristics of patients with MS and seizure recorded. Data from the literature review and from our own clinical series were combined and examined. *Results*. Of the MS patients, 1.95% experienced seizures at any time during life. Patients experiencing seizures before MS diagnosis were classified into three categories: (a) 25 (7.3% of patients with MS and seizures) with seizure as the initial presentation of MS; (b) 27 (7.9%) with seizures appearing with other signs and symptoms of MS; and (c) 68 (20%) with seizures occurring years or an unknown period of time before MS onset. Seizure occurring as a symptom of MS relapse was found in 29 patients. *Conclusion*. The prevalence of seizures among MS patients was higher than that in the general population, indicating a relationship between seizures and MS. Seizures occurred before MS diagnosis in a small percentage of patients.

Key words: multiple sclerosis, seizure, epilepsy, prevalence, neurological symptoms, magnetic resonance imaging

There is an increased prevalence of seizures in multiple sclerosis (MS) patients when compared to the general population, as demonstrated by a number of studies (Poser and Brinar, 2003; Nyquist *et al.*, 2002; Belletrutti *et al.*, 2004). The reason for this association is unknown. Rarely, MS can initially present as epileptic seizures, however, the prevalence of this phenomenon is unclear. Here, we present a case of MS presenting as a seizure and examine the occurrence of similar cases from our review of the literature, an analysis which has not previously been reported. The mean prevalence of epileptic seizures in MS patients, the prevalence of seizures presenting with MS relapse, and the possible causative relationship between MS and seizures are also discussed.

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Patients and methods

MS patients from our clinic, the Alaska Brain Center, were selected from our electronic medical record containing patients acquired over six years of private practice in neurology. These MS patients were diagnosed (or a prior diagnosis was supported) based on the revised McDonald criteria (Polman *et al*., 2005) and those with seizures were selected based on examination of medical history, with seizure diagnosis supported by EEG studies. A search of the literature provided a number of studies concerning the prevalence of seizure among MS patients and studies were selected for inclusion based on relevance *(table 1)*. These papers were carefully examined and the number of patients, diagnostic criteria, characteristics of patients presenting with MS and seizures, and possible overlap between geographical regions and time periods were determined. Prevalence of seizure among MS patients was determined by combining data from our clinic with data from the selected studies.

Case report

A 39-year-old Caucasian female was presented to the emergency room with a first generalised tonic clonic seizure and was referred to our centre in 2007. She reported an aura of visual changes, similar to "heat stroke". Seizure duration was reported to be five to six minutes. Postictal symptoms included confusion, disorientation, muscle pain, tongue biting, and fatigue. Her family history was unavailable as the patient was adopted. Medical history included depression and Raynaud's phenomenon. The patient drank two beers and smoked one pack of cigarettes per day, and reported recent stress from a lawsuit. She was taking Remeron (mirtazapine) for depression; seizure is listed among the adverse effects of Remeron. Vitamins were the only other reported medication. There were no recent vaccinations or illnesses and the neurological examination was normal.

A 41-minute electroencephalogram (EEG), during wakefulness and sleep, yielded normal results. A 1.5 Tesla MRI scan of the head with and without gadolinium showed 12 linear radiating periventricular FLAIR (fluid attenuated inversion recovery) hyperintensities in deep white matter *(figures 1* and *2)* and a solitary 7 mm focus of signal in the central thoracic cord at T4, consistent with either MS or a metastatic disease. A positron emission tomography (PET) scan indicated no evidence of neoplasm and CT of the chest, abdomen, and pelvis (CAP) was negative for malignancy.

Blood laboratory values were unremarkable except for low normal vitamin B12 (271) and undetectable vitamin B6. CSF analysis was normal except for three markers for MS: a high CSF immunoglobulin G (IgG) index (0.83, normal < 0.66), high IgG synthesis rate (+3.5, normal –9.9 to +3.3), and high myelin basic protein (5.0, normal < 4.0). The spinal fluid contained no neoplastic cells. An MRI scan of the brain six months after the initial brain MRI showed two new white matter lesions, indicating temporal spread. Thus, the patient was diagnosed with definite MS based on both Poser and revised McDonald criteria. Her seizure was diagnosed as an acute symptomatic partial complex seizure with secondary generalisation, symptomatic of an acute MS attack.

The patient was treated with levetiracetam at 1000 mg twice daily, 500 mcg vitamin B12 sublingual dots daily, vitamin D 400 units daily, 5 mg vitamin B6 daily, and subcutaneous injections of interferon beta-1a 44 mcg three times per week. As of December 2009, the patient did not report any more seizures.

Discussion

The prevalence of seizures among patients diagnosed with MS is generally accepted to be greater than the 0.4 to 0.8% estimated seizure prevalence in the general population (Poser and Brinar, 2003). In our review of the literature, we found that of 29,164 MS patients from 16 studies (including our own), 569 or 1.95% experienced seizures, a prevalence roughly 2.5 to five times higher than that in the general population *(table 1)*. Prevalence ranged from 0.89 to 7.84% in the individual studies. Only one study, Nyquist *et al*. (2001), did not show an increased prevalence of seizures in MS patients. Among the papers considered was a review by Poser and Brinar (2003) encompassing 29 clinical series; 17,239 MS cases. In addition to prevalence, a few studies examined the risk, age-adjusted incidence, and yearly incidence of seizure in MS patients; the majority of the studies concluded that the risk and incidence of seizure was higher in MS patients than in the general population, with the exception of Nyquist *et al*. (2002). Discrepancies between the respective studies could be due to differences in the diagnostic criteria for MS and epilepsy. There are also confounding factors for a correct diagnosis. The MS differential diagnosis includes demyelinating disease (*e.g*. acute disseminated encephalomyelitis, neuromyelitis optica, transverse myelitis), infections (*e.g*. Creutzfeldt-Jacob disease, *Borrelia burgdorferi*), psychiatric disease (*e.g*. conversion disorder), vascular disease (*e.g*. stroke, vasculitis, CADASIL), nutritional disorders (*e.g*. vitamin B12 deficiency), hereditary disease (*e.g*. adrenoleukodystrophy, metachromatic leukodystrophy, Fabry disease, Wilson disease), systemic autoimmune disease (*e.g*. system lupus erythematosis, sarcoidosis), and neoblastic disease (*e.g*. primary CNS

Table 1. Prevalence of seizures among MS patients.

Paper	No. MScases	No. MS patients with seizure	% MS patients with seizure	Diagnostic criteria for MS	Notes
Alaska Brain Center EMR	124	8	6.45	Revised McDonald	Clinical series
Catenoix *et al*. (2011)	5,041	67	1.3	Poser: probable and definite cases	Clinical Series. Excluded 35 patients where seizures occurred long before MS onset or where other possible causes of seizures were present.
Striano *et al*. (2003a)	270	13	4.81	McDonald	Clinical series
Nicoletti *et al*. (2003)	170	5	2.94	Poser: definite and probable cases	Population based. Age-adjusted risk of developing epilepsy was 147.8 per 100,000 person years, 3 times that of the general population. One patient had other risk factors for seizure and was excluded from the risk calculation. Excluded MS patients with acute symptomatic seizures.
Poser and Brinar (2003)	17,239	389	2.25	Not given	Review of 29 clinical series. Range of 0.5 to 10.8% in clinically diagnosed MS. Mean of 2.25%, median of 2.7%.
Sokic *et al.* (2001) **Reviewed by Poser and Brinar (2003)**	268	20	7.46	Poser: definite cases only	Clinical series
Olafsson *et al*. (1999) **Reviewed by Poser and Brinar (2003)**	188	4 epilepsy after signs and symptoms of MS	2.12	Poser: definite cases only	Population based. Excluded patients with only acute symptomatic seizures. Based on 4 patients, cumulative risk of developing epilepsy after onset of MS symptoms was 1.1% at 5 years, 1.8% at 10 yrs, 3.1% at 15 yrs. Based on 3 patients, cumulative risk of developing epilepsy after MS diagnosis was 0.5% at 5 yrs and 1.9% at 10 and 15 years, 3 times that expected in the general population.
		5 epilepsy at anytime in their lives	2.67		
Moreau *et al.* (1998) **Reviewed by Poser and Brinar (2003)**	402	17	4.23	Poser	Clinical series

Table 1. (*Continued*)

Paper	No. MS cases	No. MS patients with seizure	% MS patients with seizure	Diagnostic criteria for MS	Notes
Engelsen and Grønning (1997) **Reviewed by Poser and Brinar (2003)**	423	17	4.02	MacAlpine: definite and probable cases	Population based
Ghezzi *et al.* (1990) **Reviewed by Poser and Brinar (2003)**	1,459 definite MS	34	2.33	Unknown	Clinical series. Only the definite MS cases were included in analysis by Poser and Brinar (2003)
	518 probable MS	3	0.58		
	376 possible MS	3	0.79		
	2,353 total	40 total	1.70		
Büttner *et al.* (1989) **Reviewed by Poser and Brinar (2003)**	330	14 Total	4.24	Unknown, "Clinical and laboratory supported"	Clinical series
		6 Seizure most likely due to MS	1.82		
Kinnunen and Wikström (1986) **Reviewed by Poser and Brinar (2003)**	599	21	3.51	Schumacher Committee Criteria	Prevalence cohort
Gambardella *et al.* (2003)	350	16	4.57	Unknown	Clinical series
Eriksson *et al.* (2002)	255	20	7.84	Poser: definite and probable cases	Population based. Yearly incidence of seizures was estimated at 349/100,000/year, compared to 29-49/100,000/yr in the general population. Prevalence of first epileptic seizure in MS patients was 3.5% over 25 years, with a 15-year cumulative risk of a seizure of 3.1%.
Nyquist *et al.* (2002)	208	5 After MS diagnosis	2.40	Poser: definite cases only	Population based. Prevalence was higher than in the general population, but age-adjusted incidences were not significantly different. Age-adjusted incidence of first unprovoked seizure in Rochester, Minnesota was 61/100,000 person years. Age adjusted incidence of seizure after MS diagnosis was 61/100,000 person years. Age-adjusted incidence of seizure after first symptoms of MS was 80/100,000 person years. Age-adjusted incidence of seizure at anytime in the life of an MS patient was 82/100,000 person years.
NOTE: Possible overlap between Nyquist *et al.* (2002) and Nyquist *et al.* (2001): patients from Nyquist *et al.* (2002) were excluded in overall calculations	214	11 Seizure at anytime in their lives	5.14		
Nyquist *et al.* (2001)	5,715	51	0.89	Poser	Clinical series. Not significantly different from general population. Excluded patients diagnosed with epilepsy before MS.
Total # patients	29,164	569	1.95		

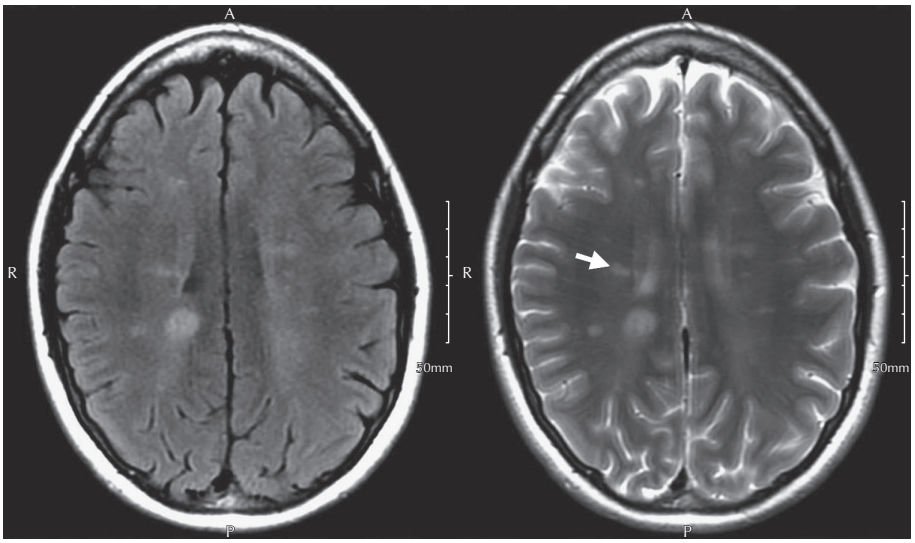

Figure 1. FLAIR and T2W axial images demonstrate multiple deep white matter hyperintensities. Note the radial pattern to many of these lesions, indicated by the arrowhead.

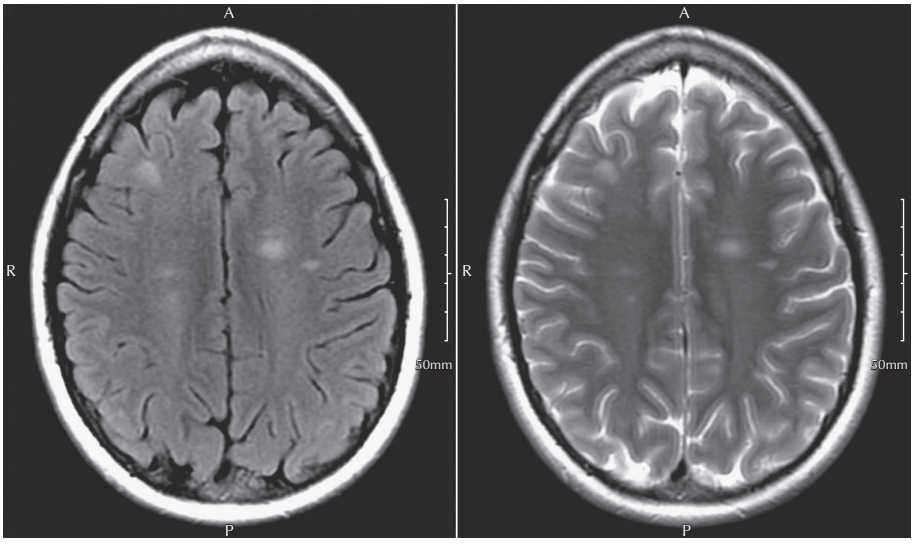

Figure 2. FLAIR and T2W axial images demonstrate hyperintensities in the right frontal and left frontal white matter.

lymphoma, paraneoplastic syndromes) (Miller *et al*., 2008). The differential diagnosis for epilepsy includes convulsive syncope and pseudoseizures. Additionally, differences among criteria for patient inclusion and possible biases based on patient selection were noted. The diagnostic criteria and patient selection for each paper are summarised in *table 1*.

Reports of cases presenting with seizure as an initial symptom of MS, similar to our patient, are rare. The frequency among previous studies is difficult to determine; many excluded patients with acute symptomatic seizures and others did not consider how long the seizures appeared before or after other signs and symptoms of MS. We identified 15 papers, in addition to our own, in which the time seizures developed was considered, totalling 341 cases of seizure coincident with MS *(table 2)*. We classified the cases into three categories based on the commonly encountered descriptions: (a) acute symptomatic or leading to MS diagnosis (seizure as the initial presentation of MS); (b) appearing with other signs and symptoms of MS but before MS diagnosis; and (c) occurring some time or an unknown period of time before MS diagnosis.

In category (a), 25 cases of seizure as the initial presentation of MS were included. These 25 patients represented 7.3% of the 341 patients with MS and

Table 2. Seizures as an initial presentation of MS.

Seizure classification	Paper	No. of cases	% of MS + seizure cases	Total MS +seizure cases	Specific description
(a) Acute symptomatic or leading to MS diagnosis (initial presentation)	Alaska Brain Center EMR	2	25	8	
	Catenoix, *et al.* (2011)	7	10	67	Initial clinical manifestation
	Striano *et al.* (2003b)	2	15	13	Acute symptomatic
	Nyquist *et al.* (2001)	3	5.9	51	Seizure led to diagnosis
	Gambardella *et al.* (2003)	5	31	16	Temporal lobe epilepsy as the unique manifestation of MS
	Gurtubay *et al.* (2000)	2	29	7	Part of first MS episode
	Olafsson *et al.* (1999)	1	25.0	4	Excluded patients with *only* acute symptomatic seizures
	Moreau *et al.* (1998)	2	12	17	First symptom of MS
	Bolay *et al.* (1995)	1	N/A	1	Admitted for seizure
Total for the category		25	14	184	
Total overall		25	7.3	341	
(b) Appears with other signs and symptoms but before MS diagnosis	Nyquist *et al.* (2001)	11	22	51	After other signs and symptoms of MS
	Gurtubay *et al.* (2000)	3	43	7	Part of first episode
	Engelsen and Grønning (1997)	4	24	17	Coincidentally with MS onset. 1 patient *may* have had a seizure 15 years before
	Okada *et al.* (1991)	2	N/A	2	
	Ghezzi *et al.* (1990)	4	10	40	Coinciding with other signs and symptoms
	Kinnunen and Wikström (1986)	3	14	21	Part of neurological symptoms occurring at the first bout of MS

Table 2. (*Continued*)

Seizure classification	Paper	No. of cases	% of MS + seizure cases	Total MS +seizure cases	Specific description
Total for the category		27	20	138	
Total overall		27	7.9	341	
(c) Occurred years or an unknown amount of time before MS Diagnosis NOTE: Possible overlap between Nyquist (2002) and Nyquist (2001)	Alaska Brain Center EMR	1	13	8	1 year before diagnosis
	Catenoix, *et al.* (2011)	26	39	67	Mean time between first seizure and MS onset 18.8 ± 10.9 years, range 2-44. No possible cause other than MS identified
	Striano *et al.* (2003a)	1	7.7	13	16 years before diagnosis
	Nicoletti *et al.* (2003)	1	20	5	8 years before MS diagnosis, other epilepsy risk factors. Excluded MS patients with acute symptomatic seizures
	Eriksson *et al.* (2002)	1	5	20	Years before MS diagnosis, excluded from incidence calculations (*table 1*).
	Nyquist *et al.* (2002)	6	55	11	Anytime before MS diagnosis. **Excluded due to overlap.**
	Nyquist *et al.* (2001)	11	18	62	Patients diagnosed with epilepsy before MS, excluded from analysis in *table 1*.
	Sokic *et al.* (2001)	4	20	20	1-5 years before other signs and symptoms.
	Ghezzi *et al.* (1990)	13	33	40	Anytime before diagnosis.
	Kinnunen and Wikström (1986)	10	48	21	Before MS symptoms.
Total for the category		68	27	256	
Total overall		68	20	341	
Total MS + seizure cases				341	

epilepsy (Catenoix *et al.*, 2011; Striano *et al.*, 2003a, 2003b; Gambardella *et al.*, 2003; Olafsson *et al.*, 1999; Moreau *et al.*, 1998; Nyquist *et al.*, 2001; Gurtubay *et al.*, 2000; Bolay *et al.*, 1995), ranging from 5.9 to 29% in each of the respective papers.

In category (b), a total of 27 patients (from six studies) with seizures appearing with other signs and symptoms of MS but before diagnosis were included (Kinnunen and Wikström, 1986; Ghezzi *et al.*, 1990; Engelsen and Grønning, 1997; Nyquist *et al.*, 2001; Gurtubay *et al.*, 2000; Okada *et al.*, 1991). These 27 patients represented 7.9% of the 341 total MS and seizure cases, ranging from 10.0 to 43% in each of the respective papers. One of the patients presented by Engelsen and Grønning (1997) may have experienced a seizure many years before and thus may be incorrectly classified. Excluding this patient decreases the percent of patients represented by category (b) to 7.6%.

In category (c), 68 patients with seizures occurring years (one to 44) or an unknown period of time before MS onset were included; 20% of the 341 patients with MS and seizures, ranging from 5 to 55% in the individual papers (Catenoix *et al.*, 2011; Nicoletti *et al.*, 2003; Eriksson *et al.*, 2002; Nyquist *et al.*, 2002; Ghezzi *et al.*, 1990; Striano *et al.*, 2003a; Sokic *et al.*, 2001; Kinnunen and Wikström, 1986; Nyquist *et al.*, 2001). We included these patients as it is possible that the seizures were due to undiagnosed MS and could have coincided with undetected MS lesions. These patients could also be considered to have the MS variant radiologically isolated syndrome (RIS). The study by Catenoix *et al.* (2011) specifically excluded 35 patients whose seizures occurred a long time before MS onset or whose seizures could be attributed to a cause other than MS.

Differences in the description and classification of seizures based on the temporal relationship between MS and epilepsy may have led to the miscategorisation or exclusion of patients. In particular, many papers did not specifically mention whether seizures occurred with, before, or after other signs and symptoms of MS. Due to a one-year overlap between the reports of Nyquist *et al.* (2001) and Nyquist *et al.* (2002) in the same geographical area, we did not consider the patients mentioned by the smaller study, Nyquist *et al.* (2002), and a few cases may have been omitted as a result. Olafsson *et al.* (1999) excluded patients presenting with only acute symptomatic seizures, therefore including the data from this paper skewed our results slightly. Gambardella *et al.* (2003) were primarily interested in the five cases presenting with temporal lobe epilepsy as the only clinical manifestation of MS at any time and thus may not have mentioned other cases with seizure at MS onset. Many papers were simply case studies and offer us no information on the prevalence among their own cohort of MS patients.

Seizure has also been observed as a symptom and often the only clinical manifestation of MS relapse, as determined by the revised McDonald criteria (Polman *et al.*, 2005). We found 29 patients with seizure co-occurring with new MS lesions in our review *(table 3)*. An increased incidence of status epilepticus (SE) among MS patients, ranging from 17.6 to 38.4%, was noted in multiple studies (Catenoix *et al.*, 2011; Engelsen and Grønning, 1997; Moreau *et al.*, 1998; Sokic *et al.*, 2001; Striano *et al.*, 2003a), compared to an incidence of 2-10% in the general population of epilepsy patients (Shorvon, 1994). Due to the serious nature of SE, initiating antiepileptic treatment after the first seizure was recommended by three reports (Catenoix *et al.*, 2011; Engelsen and Grønning, 1997; Striano *et al.*, 2003a).

The nature of the association between MS and epileptic seizures is unclear. Cortical and subcortical MS lesions have been implicated as a possible source of seizures (Sokic *et al.*, 2001; Moreau *et al.*, 1998; Spatt *et al.*, 2001; Truyen *et al.*, 1996). This may be due to lesions acting as foci for epileptic activity or a result of surrounding oedema (Belletrutti *et al.*, 2004; Poser and Brinar, 2003; Gandelman-Marton *et al.*, 2003; Spatt *et al.*, 2001). Specifically, Thompson *et al.* (1993) suggested that seizures are caused by oedema in relapsing-remitting MS, since seizures occur only at MS onset/relapse, whereas the continuing seizures in primary-progressive MS cases are due directly to large, constant lesions. Differential expression of neuronal sodium channels due to demyelination or other damage has also been observed (Poser and Brinar, 2003; Striano *et al.*, 2003a). Seizures may also be attributed simply to general metabolic changes (Striano *et al.*, 2003a; Gandelman-Marton *et al.*, 2003; Chabolla *et al.*, 1996; Thompson *et al.*, 1993), and two of the studies suggested that MS acts solely as a trigger for potential idiopathic epilepsy due to a disruption of the cerebral environment (Poser and Brinar, 2003; Belletrutti *et al.*, 2004). Poser and Brinar (2003) supported this explanation, arguing that although seizures are rare in MS patients, cortical and subcortical plaques are not, and thus the plaques themselves seem unlikely to be the direct source. Some researchers are not convinced that the relationship is not merely a coincidence (Poser and Brinar, 2003; Belletrutti *et al.*, 2004). However, the majority of the studies reviewed concluded that coincidence was unlikely, proposing that brain lesions of any sort are a likely risk factor for seizure and epilepsy.

The authors of this study propose that the association between MS and epilepsy is based on the

Table 3. Seizure as a symptom of MS relapse.

Paper	No of patients	% of patients with MS + seizure, n	Characteristics
Catenoix *et al*. (2011)	4	6.0, 67	
Belletrutti *et al*. (2004)	1	N/A, 1	Only manifestation
Striano *et al*. (2003b)	1	7.7, 13	Only manifestation
Gandelman-Marton *et al*. (2003)	1	N/A, 1	EEG showed PLEDs (periodic lateralised epileptiform discharges) in right temporal region
Sokic *et al*. (2001)	8	40, 20	Only manifestation in 2.10%
Moreau *et al*. (1998)	7	41, 17	Only clinical manifestation of new active lesion
Chabolla *et al*. (1996)	1	N/A, 1	2 separate relapses, recurrent PLEDs present
Thompson *et al*. (1993)	6	N/A, 6	Only clinical manifestation of relapse in 3
Total	29	23, 126	

focal disruption of physiological activity (delay or block of action potentials, hypersynchronisation of neuron clusters) due to physical damage to myelin and axons, particularly in cortical and subcortical areas of the brain. Kharatishvili and Pitkänen (2010) reported a correlation between the severity and extent of cortical injury and seizure activity in rats with traumatic brain injury, noting increased hyperexcitability and epileptogenicity. Neuron irritability (cell depolarisation due to immune-mediated membrane permeability) is another possible process that may facilitate abnormal epileptogenic activity. Cell and axon damage results from immunologically mediated processes (antibodies, lymphokines, and cytokines). Seizures have also been observed as an unusual presentation of the white matter disease, X-linked adrenoleukodystrophy (Xiong *et al*., 2003).

Conclusion

We present a case study of seizure as an initial symptom of MS and a review of the literature in order to examine the co-prevalence between MS and seizure. The number of patients presenting with seizures at the onset of MS was quantified. Our findings indicate that seizures are more common in MS patients than in the general population, with a mean co-prevalence of 1.95% *(table 1)*. Seizure was reported as a symptom of MS before MS diagnosis: (a) as the initial presentation of MS in 7.3% of 341 patients; (b) with other signs and symptoms of MS in 7.9%; and (c) occurring some time or an unknown period of time before MS diagnosis in 20% *(table 2)*. We also found 29 cases in which seizure was associated with a relapse of MS. We conclude that seizure occurs in 1.95% of MS patients for whom seizure is the only symptom at MS onset in 7.3%. Thus, MS should be considered in the differential diagnosis when a convulsion occurs. Possible explanations for the association between MS and seizures encountered in the literature include neuronal changes, disruption of cerebral environment-triggering latent epilepsy, or direct causation of seizures by lesions or oedema. The authors of this study favour causation of seizure activity by disruption of physiological activity due to physical damage and/or neuronal irritability and damage due to immune processes.

Disclosure

None of the authors has any conflict of interest to disclose.

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