SEIZURE AS A MANIFESTATION OF MULTIPLE SCLEROSIS: A CASE REPORT AND LITERATURE REVIEW

or

MULTIPLE SCLEROSIS PRESENTING AS SEIZURE

Key Words: Multiple sclerosis, Seizure, Epilepsy, Prevalence, Neurologic symptoms, Magnetic Resonance Imaging

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ABSTRACT

Background: The incidence of seizures is generally accepted as greater in multiple sclerosis (MS) patients than in the general population. Rarely MS can present initially as seizure. ***Objective:*** To present a case report of seizure as the initial symptom of MS, to quantify the occurrence of seizure among MS patients, and to classify patients according to when seizures occurred relative to MS onset. ***Methods:*** The number of MS patients treated by our clinic and the histories of the patients presenting with MS and seizure were examined. Twenty-four scientific papers were reviewed and the number and characteristics of the patients recorded. Data from the literature review and from our own clinical series were combined for analysis and incorporated into the tables. ***Results:*** 2.08% of MS patients experienced seizures at any time in their lives. Patients experiencing seizures before MS diagnosis were classified into three categories: (a) 18 (7.1% of patients with MS and seizures) with seizure as the initial presentation of MS, (b) 24 (9.5%) with seizures appearing with other signs and symptoms of MS, and (c) 42 (17%) with seizures occurring years or an unknown period of time before MS onset. Seizure occurring as a symptom of an MS relapse was found in 25 patients. ***Conclusion:*** The prevalence of seizures among MS patients is higher than that in the general population, indicating a relationship between seizures and MS. Seizure occurs before MS diagnosis in a small percentage of patients.

Introduction

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 source for this association is unknown. Rarely, MS can present initially 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 done. The mean prevalence of epileptic seizures in MS patients, the prevalence of seizures presenting with an MS relapse, and the possible causative relationship between MS and seizures are also discussed.

Patient and Methods

MS patients from our clinic, the Alaska Brain Center, were selected from our electronic medical record containing patients acquired over 6 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). Those with seizures were chosen by examination of their histories, 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, studies were selected for inclusion based on relevance (Table 1). These papers were carefully examined to determine numbers of patients, diagnostic criteria, characteristics of those patients presenting with MS and seizures, and possible overlap

between regions and time periods. Prevalence of seizure among MS patients was determined by combining data from our clinic with data from the selected studies.

Case Report

The patient was a 39 year old Caucasian female who presented to the ER with a new onset generalized tonic clonic seizure and was referred to our office in 2007. She reported an aura of vision changes, similar to “heat stroke”. Seizure duration was reported as 5 to 6 minutes. Post-ictal symptoms included confusion, disorientation, muscle pain, a bitten tongue, and fatigue. Her family history was unavailable, as the patient was adopted. Past medical history included depression and Raynaud’s phenomenon. The patient drank two beers daily, smoked one pack per day, and reported recent stress from a lawsuit. She was taking Remeron (mirtazapine) for depression. Seizure is listed among Remeron’s adverse effects. Vitamins were the only other reported medications. There were no recent vaccinations or illnesses and the neurological exam was normal.

A 41 minute awake and asleep electroencephalogram (EEG) yielded normal results. A 1.5 Tesla MRI of the head with and without gadolinium showed 12 linear radiating periventricular FLAIR (fluid attenuated inversion recovery) hyperintensities in deep white matter (Figure 1-2) and a solitary seven 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 for neoplasm and a 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 of the brain 6 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 the Poser and Revised McDonald Criteria. Her seizure was diagnosed as an acute symptomatic partial complex seizure with secondary generalization, 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 44mcg three times per week. As of December 2009 the patient has reported no more seizures.

Discussion

The prevalence of seizures among patients diagnosed with MS is generally accepted as 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 24,123 MS patients from 15 studies (including our own), 502 or 2.08% experienced seizures, a prevalence 2.5 to five times higher than that in the general population (Table 1). The percentages 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 incidences, and yearly incidences of seizure in MS patients; the majority of the

studies concluded that the risk and incidences of seizure were 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 diagnois. The MS differential diagnosis includes diabetes mellitus, hypertension, vitamin B12 deficiency, CADASIL, age related microvascular disease, and vasculitis. 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. Table 1 summarizes the diagnostic criteria and patient selection for each paper.

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 exclude patients with acute symptomatic seizures, others do not discriminate based on how long before or after other signs and symptoms of MS the seizures appeared. We found 14 papers, in addition to our own, which differentiated based on when seizures developed, totaling in 253 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.

Category (a) contained 18 cases of seizure as the initial presentation of MS. These 18 patients represented 7.1% of the 253 patients with MS and epilepsy (Striano *et al.,* 2003a and b; Gambardella *et al.,* 2003; Olafsson *et al.,* 1999; Moreau *et al.,* 1998; Nyquist

et al., 2001; Gurtubay *et al.*, 2000; Bolay *et al.*, 1995). The individual percentages ranged from 5.9% to 29%.

In category (b), five papers presented a total of 24 patients with seizures appearing with other signs and symptoms of MS but before diagnosis (Ghezzi *et al.*, 1990; Engelsen and Grønning, 1997; Nyquist *et al.*, 2001; Gurtubay *et al.*, 2000; Okada *et al.*, 1991). These 24 patients represented 9.5% of the 253 total MS and seizure cases, ranging from 10.0% to 43% in 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 would decrease the percent represented by category (b) patients to 9.1%.

Category (c) contains 42 patients with seizures occurring years (one to 16) or an unknown period of time before MS onset, 17% of the 253 patient with MS and seizures, ranging from 5% to 55% in the individual papers (Nicoletti *et al.*, 2003; Eriksson *et al.*, 2002; Nyquist *et al.*, 2002; Ghezzi *et al.*, 1990; Striano *et al.*, 2003b; 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).

Differences in the description and classification of seizures based on the temporal relationship between MS and epilepsy may have led to the miscategorization or exclusion of patients. Specifically, 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 of Nyquist *et al.* (2001) and Nyquist *et al.* (2002) in the same geographic area, we did not

count 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 of an MS relapse, and often as the only clinical manifestation. We found 25 patients with seizure co-occurring with new MS lesions in our review (Table 3).

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 it may be a result of surrounding edema (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 edema 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 the 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.*, 2003b). Seizures may also be attributed simply to general metabolic changes (Striano *et al.*, 2003b; 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 of MS and epilepsy is based on the focal disruption of physiological activity (delay or block of action potentials, hypersynchronization of neuron clusters) due to physical damage to myelin and axons, particularly in cortical and subcortical areas of the brain. Kharatishvili and Pitkänen (2010) report a correlation of the severity and extent of cortical injury to seizure activity in rats with traumatic brain injury, noting increased hyperexcitability and epileptogenicity. Neuron irritability (cell depolarization 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, cytokines). Seizures have also been observed as an unusual presentation the white matter disease X-linked adrenoleukodystrophy (Xiong *et al*., 2003).

Conclusion

We have presented a case study of seizure as an initial symptom of MS, reviewed the literature to examine the co-prevalence between MS and seizure, and quantified the

number of patients presenting with seizures at the onset of MS. Our findings provide support for the general consensus that seizures are more common in MS patients than in the general population, with a mean co-prevalence of 2.08% and a range of 0.89% to 7.84%, as expressed by the percentage of MS patients experiencing seizures (Table 1). Cases of seizure occurring as an initial symptom of MS were classified into three categories and quantified (Table 2): (a) seizure as the initial presentation of MS in 18 of 253 patients (7.1%), (b) seizures appearing with other signs and symptoms of MS but before MS diagnosis in 24 of 253 patients (9.5%), and (c) seizures occurring some time or an unknown period of time before MS diagnosis, found in 42 of 253 patients (17%). We also found 25 cases in which seizure was associated with an MS relapse. Possible explanations for the connection between MS and seizures encountered in the literature include coincidence, neuronal changes, disruption of the cerebral environment triggering latent epilepsy, or direct causation of seizures by MS lesions or surrounding edema. The authors of this study favor causation of seizure activity by disruption of physiological activity due to physical damage and/or neuronal irritability and damage due to immune processes. We conclude that seizure does occur in 2.08% of MS patients, at the onset of MS in 7.1%, and thus MS should be considered in the differential diagnosis when a convulsion occurs.

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Table 1: Prevalence of seizures among MS patients

Paper	No. MS cases	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.
Striano *et al.* (2003)b	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 S&S of MS* *5 epilepsy at anytime in their lives*	2.12% 2.67%	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 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 general population.

Moreau *et al.* (1998) **Reviewed by Poser and Brinar (2003)**	*402*	*17*	4.23%	Poser	Clinical series.
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)**	*1459 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%		
	2353 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%	Unknown, "clinically definite"	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 as 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 1st unprovoked seizure in Rochester, Minn = 61/100,000 person years. Age adjusted incidences of seizure after MS diagnosis = 61/100,000 person years. Age-adjusted incidences of seizure after first symptoms of MS = 80/100,000 person years. Age-adjusted incidence of seizure at anytime in the life of an MS patient = 82/100,000 person years.
NOTE: Possible overlap of Nyquist et al. (2002) and Nyquist *et al.* (2001) – Excluded patients from Nyquist *et al.* (2002) in overall calculations	214	11 Seizure at anytime in their lives	5.14%		
Nyquist et al. (2001)	5715	51	0.89%	Poser	Clinical series. Not significantly different from general population. Excludes patients diagnosed with epilepsy before MS.
Total # patients	**24123**	**502**	**2.08%**		

Table 2: Seizures as an initial presentation of MS

Seizure Classification	Paper	No. of Cases	% of MS + Sz Cases	Total MS+Sz Cases	Specific Description
(a) Acute symptomatic or leading to MS diagnosis (initial presentation)	Alaska Brain Center EMR	2	25%	8	
	Striano *et al.* (2003)b	2	15%	13	Acute symptomatic
	Nyquist *et al.* (2001)	3	5.9%	51	Seizure led to diagnosis
	Olafsson *et al.* (1999)	1	25.0%	4	Excluded pts 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
	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
Total for the category		**18**	15%	117	
Total Overall		**18**	**7.1%**	**253**	
(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
	Okada *et al*. (1991)	2	N/A	2	
	Ghezzi *et al.* (1990)	4	10%	40	Coinciding with other S&S
	Engelsen and Grønning (1997)	4	24%	17	Coincidentally with MS onset. 1 pt *may* have had a seizure 15 years before.
	Gurtubay *et al.* (2000)	3	43%	7	Part of first episode
Total for the category		24	21%	117	
Total Overall		**24**	**9.5%**	**253**	
(c) Occurred years or an unknown amount of time	Alaska Brain Center EMR	1	13%	8	1 year before diagnosis
	Striano *et al.* (2003)b	1	7.7%	13	16 years before diagnosis

before MS 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).
NOTE: Possible overlap between Nyquist (2002) and Nyquist (2001)	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 S&S
	Ghezzi *et al*, (1990)	13	33%	40	Anytime before diagnosis
	Kinnunen and Wikström (1986)	10	48%	21	Before MS symptoms
Total for the category		42	22%	189	
Total Overall		**42**	**17%**	**253**	
Total MS + Seizure Cases				**253**	

Table 3: Seizure as a symptom of an MS relapse

Paper	No of patients	% of MS + Sz pts, n	Characteristics
Belletrutti *et al.* (2004)	1	N/A, 1	Only manifestation
Striano *et al.* (2003)b	1	7.7%, 13	Only manifestation.
Gandelman-Marton *et al*. (2003)	1	N/A, 1	EEG showed PLEDs (periodic lateralized 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	**25**	**42%, 59**	

Figure Legends

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

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

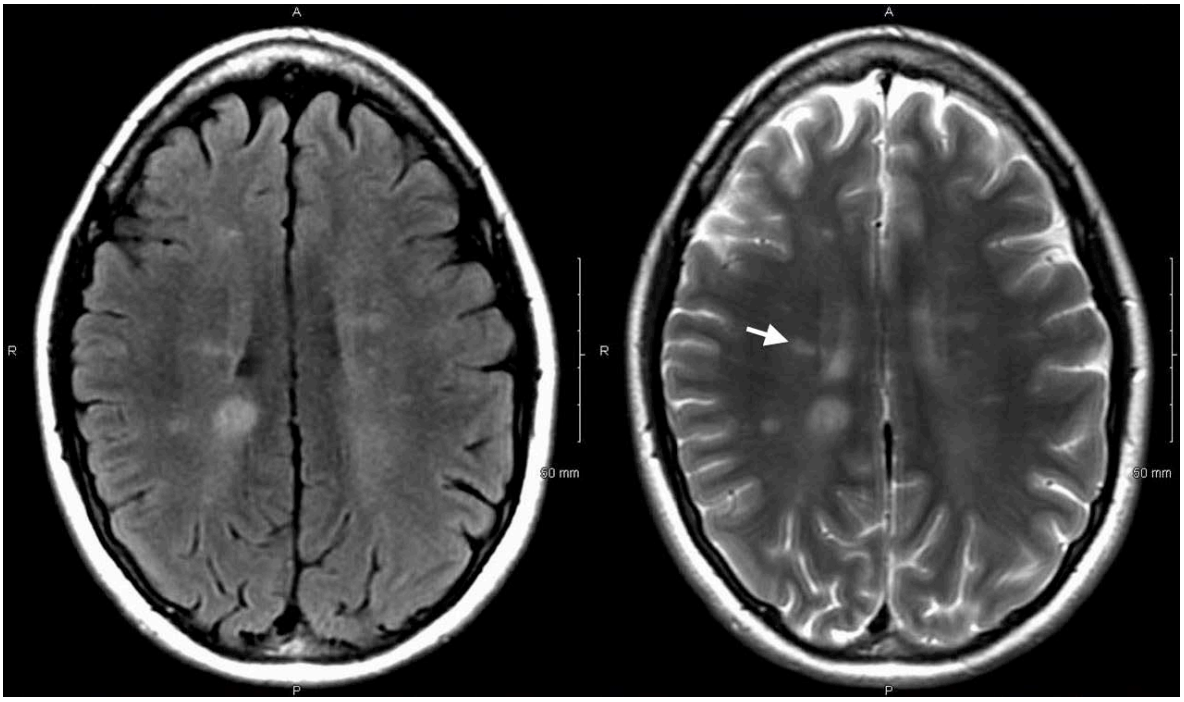
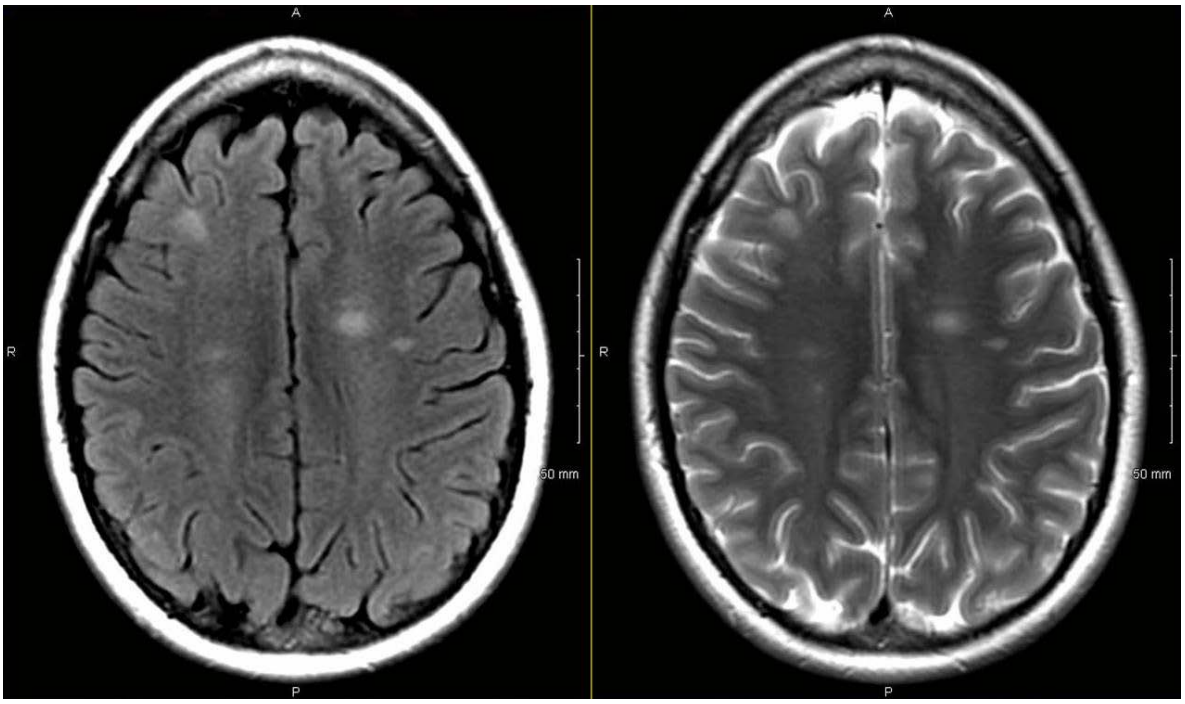


Figure 1. FLAIR and T2W axial images demonstrate multiple deep white matter hyperintensities. Note the radial pattern to many of these lesions, indicated by arrowhead.



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