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Seizures in Patients with Multiple Sclerosis: Epidemiology, Pathophysiology and Management

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Abstract

Seizures have been recognized to occur in multiple sclerosis since early descriptions of the disease. Various studies have attempted to determine the incidence and prevalence of seizures in multiple sclerosis; although they differ in the reported prevalence, seizures do appear to be more common in multiple sclerosis cohorts than in the general population.

The pathological underpinning of seizures in multiple sclerosis remains indeterminate. Cortical and subcortical demyelination and inflammation may explain the increased frequency of seizures in multiple sclerosis, although this hypothetical correlation remains to be proven.

Management of seizures in multiple sclerosis is similar to the management of seizures in other patients. Consideration of the underlying neurological deficits related to multiple sclerosis may be necessary, and dosages should be adjusted if increased sensitivity to antiepileptic side effects or interaction with other centrally-acting medications is suspected. The prognosis of epilepsy in patients with MS remains uncertain, with some studies suggesting a more favorable prognosis than others.

Keywords

Multiple sclerosis; seizure; epilepsy

Introduction

Multiple sclerosis (MS) is a disease of the central nervous system having both inflammatory and chronic degenerative components. Multifocal central nervous system lesions affect diverse brain regions at unpredictable intervals. Acute episodes of demyelination and axonal injury may involve local inflammatory and destructive processes. The underlying etiology of the disease remains elusive, and the triggers of demyelination as well as the propagation of the disease over time remain unexplained..

Seizures have been recognized to occur in MS since the earliest descriptions of this disease [1] and were included in textbook descriptions of MS symptoms for over 125 years.[2] Since that time, seizures have been reported in many clinical descriptions of the disease. Recent descriptions of the pathological findings associated with MS, including increased appreciation of cortical and subcortical demyelination with and without inflammation, have shed light onto possible explanations of why seizures may be more common in MS than in the general population.

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Search Strategy

We made a systematic search of the literature relating to seizures and epilepsy in multiple sclerosis patients. MEDLINE and PubMed were employed as search engines, using the keywords "multiple sclerosis" AND ("seizure" OR "epilepsy"). We retrieved and reviewed pertinent articles regarding the epidemiology, pathophysiology and management of seizures in MS patients. The bibliographies of these papers were also reviewed to identify additional relevant publications. Studies were reviewed, and those employing current diagnostic criteria for MS were reviewed further. Some older studies returned in this search described non-epileptic paroxysmal events (e.g. tonic spasms, paroxysmal choreoathetosis, etc.) that may mimic epileptic seizures. Studies employing definitions that would result in these events being counted as seizures were excluded.

Epidemiology

The epidemiology of seizures in MS has been the subject of numerous investigations, with incomplete consensus among the reported findings. A number of methodological considerations regarding the diagnosis of MS, differences in patient inclusion and exclusion criteria and lack of control for possible confounding variables likely account for this variability. Some studies have included patients whose seizures predated the diagnosis of MS, while other studies have excluded these patients. Diagnostic criteria for MS have undergone considerable change over time.[3] The advent of the widespread use of magnetic resonance imaging (MRI) has changed not only the implementation of clinical and research diagnostic criteria, but also has advanced and complicated our conceptions regarding the pathological processes of demyelinating disorders. Some medications frequently prescribed in MS for non-seizure indications may increase the incidence of seizures (e.g. baclofen), while others (such as carbamazepine) may reduce this incidence.

Older studies attempting to estimate prevalence did not include currently accepted diagnostic criteria,[3] did not have MRI available and may have included some nonepileptic events as "seizure." These older studies are not included in this review, and the discussion that follows is based upon studies published after 1986. Several older studies are cited here for the interested reader.[4–18]

Population-based studies

Six population-based studies based on defined geographic boundaries have reported variable findings.[19–24] Overall, these studies have included 1,843 MS patients, of whom 70 (3.8%) had epilepsy. Excluding eleven patients who developed epilepsy prior to the diagnosis of MS, [21] 59 patients (3.2%) in the collected studies developed epilepsy after the onset of MS. These studies individually estimated standardized incidence ratios (SIRs) of 3.0[24], 3.3[22], 1.3 [23] and 7.8[20]. Calculated prevalence rates of these individual studies are listed in Table 1, and the average of these individual prevalence rates is 3.1%. Despite variability among the studies, taken together they suggest that 3–4% of MS patients will experience seizures, and despite variable techniques used to estimate age-adjusted prevalence, the age-adjusted prevalence is about 3-fold higher than that of the general population.

Hospital-based series

Seven hospital-based studies, with differing biases in ascertainment, have reported prevalence estimates ranging from 1.8% to 7.5%. Again, most values fall in the range of 2–4%, with an average of 4.1%. The details of these are included in Table 2. It is unclear why one study from Yugoslavia reported a 7- to 8-fold increased risk of seizures,[25] but this estimate is clearly

much higher than those of the other hospital or population-based studies. Excluding the outliers in Tables 1 and 2, a reasonable estimate of the prevalence rate is about 3–4%.

Many MS patients are on medications to address symptoms caused by this multifocal central nervous system disease, which may individually or collectively impact seizure frequency. Some MS patients may be on antiepileptic medications to treat other common symptoms of MS, such as pain, tonic spasms, migraine or depression, while others may be on medications reported to be associated with increased seizure frequency, as discussed below. The impact upon observed incidence and prevalence of epilepsy of these and other factors have not been controlled for in these epidemiologic studies, perhaps due to the limited number of patients that are available to conduct a study.

Relation of other medications to seizure frequency

Interferon-β medications and glatiramer acetate

Injection preparations of interferon- β_{1a} (IFN- β_{1a}) and interferon- β_{1b} (IFN- β_{1b}) are widely used for the treatment of relapsing-remitting multiple sclerosis. Each of the currently available interferon medications lists seizure as an infrequent, but serious, adverse event. The packaging insert for Avonex reports that seizures occurred in four patients receiving the drug and in no patients in the placebo arm. Convulsions were reported as adverse events in the pivotal clinical trials of both preparations of IFN-B1a. The packaging insert for weekly intramuscular interferon- β 1a (Avonex) reported that in the pivotal clinical trials, four subjects in the 351member active treatment arms experienced convulsions, compared to zero in the 333-subject placebo arms.[26] Three of these four patients had no prior seizure history. The packaging insert for the subcutaneous IFN-\beta1a preparation (Rebif) reported convulsions in 5% of subjects receiving the 22-mcg dosage, 4% in the 44-mcg treatment arm and 2% in the placebo arm. [27] No convulsions were reported in the pivotal trial of IFN- β 1b (Betaseron), but convulsions were noted in post-marketing follow-up.[28] Based upon these data, the relationship of seizures and IFN- β medications is regarded as indeterminate. The manufacturers of both IFN- β 1b medications publish a caveat that seizures have been reported in some patients using IFN-β1b and that seizures are more frequent in MS patients. The packaging insert for glatiramer acetate (Copaxone) lists convulsions as an "infrequent" adverse event in clinical trials, meaning an estimated frequency of less than 1/100 and greater than 1/1000.[29]

Baclofen

GABA-B agonists such as baclofen have a complex and incompletely understood impact upon animal models epilepsy.[30] In humans, seizures have been reported both in overdose and withdrawal of oral baclofen.[31,32] A series comparing 99 MS patients treated with intrathecal baclofen with a control group of 99 MS patients (46 of whom received oral baclofen as a symptomatic treatment) reported a significantly increased rate of epilepsy in association with the use of intrathecal baclofen (7% versus 1%).[33] Two patients in this series developed nonconvulsive *status epilepticus*, which had been previously reported in association with baclofen use in MS patients.[34]

Aminopyridines

Studies of aminopyridines have been complicated by the manifestations of seizure as an adverse event, particularly at higher dosages.[35–39] These compounds have remained an area of active interest, and one group attempted to determine MRI parameters useful in identifying MS patients at increased risk of seizure, as these patients might be inappropriate subjects for clinical trials placing them at higher risk for seizure.[40] The recent reports that 4-aminopyridine may provide symptomatic benefit for MS patients further heightens the relevance of advancing our understanding of seizures in MS.[36–38] These drugs are not presently approved by the FDA,

Clinical Features

Both partial and complex seizures have been described in MS cohorts. Some unusual seizure semiologies, such as aphasic *status epilepticus*[41] and musicogenic epilepsy,[42] have also been described in MS patients. Seizure can sometimes be the first symptomatic manifestation of MS; one series reported five patients with temporal lobe epilepsy,[43] and another reported *epilepsia partialis continua*[44] as the first clinical manifestation of MS. Although these presentations do occur, it is felt that epilepsy is rarely the heralding symptom of MS.

In a series of 51 patients with MS and seizure, 35 had generalized tonic-clonic (GTC) seizure, 14 of whom had confirmed secondary generalization. Seven had complex partial seizures, four had simple partial seizure and five (9.8%) had indeterminate seizure class.[45] Similarly, other series report a variety of semiologies, including both partial seizures and generalized seizures. Some studies suggest that partial seizures are more common than generalized seizures, [21, 22,46,47] while others[45,48,49] suggest the opposite. In studies suggesting that partial seizures are more common, there is a high frequency of secondary generalization, and in those suggesting that generalized seizure is more common, it is seldom specified whether these seizures were primarily generalized or secondarily following partial onset. Thus, the bulk of data suggests that partial seizures are more common in MS patients, accounting for over 67% of seizures[21,22,47] and that secondary generalization of these partial onset seizures may also be common.

Of interest, most authors have not found an association between epileptic seizures and the severity or duration of MS. This may shed light on the underlying mechanism of seizures in MS. Many of the studies presented in Table 1 report the mean duration between the onset of MS and the onset of epilepsy, listed in the fifth column in those tables. After exclusion of patients whose seizures predated the diagnosis of MS and the inclusion of a study of seven patients with seizures and MS,[49] analyzable data on 77 patients exists. The mean duration from onset of MS to onset of seizures was 6.8 ± 6.1 years (median 5 years, range 0–23 years). Whether seizures preceding the diagnosis of MS represent an uncommon first symptomatic exacerbation or whether these seizures were unrelated to MS is unclear. Despite this observation, the reports of seizure as the first symptomatic attack of MS taken together with the data from these epidemiologic studies suggest that seizures can occur at any point during the course of MS including early in the course of the disease. Several epidemiologic reports include both patients with relapsing-remitting MS (RRMS) as well as progressive MS, suggesting that seizure occurs in both. Few studies include sufficient clinical detail to distinguish patients having primary progressive MS (PPMS), and the prevalence of seizures in PPMS must be regarded as unknown.

Diagnostic criteria for pediatric onset multiple sclerosis have undergone substantial changes over time, complicating interpretation of earlier studies and their applicability to more recently defined case definitions. Several studies reported since 2002 have reported seizures in pediatric multiple sclerosis cohorts, and these show considerable variability. During the course of MS, symptomatic epilepsy was reported in nine patients (33%).[50] Generalized epilepsy was reported to occur in 10% (3 patients),[51] Three patients (4.5%) of a Russian cohort of MS patients with onset younger than 16 years exhibited seizures.[52] In another series of 17 pediatric MS patients, none had seizures.[53] Taken together, these studies suggest that seizures may occur at higher rates in pediatric MS patients, although studies employing more uniform diagnostic criteria may establish the frequency more accurately.

Paraclinical Investigations of Seizures in MS

Electroencephalography (EEG)

Several studies have commented on EEG abnormalities in MS patients with seizures. These findings are summarized in Table 3. Interpretation of these studies is difficult, as the timing of EEG in relation to seizure and in relation to the onset of epilepsy varies both within and among studies. In general, these studies identified EEG abnormalities in most patients with seizures. However, no available data support whether similar abnormalities in EEG would be present in MS patients without a history of seizures. These studies have important methodological differences (as discussed above) that could easily account for the different frequencies of epileptiform EEG findings that they report. Generalization from the available data is limited to the statement that most patients do have abnormalities identified on EEG and no single EEG abnormality has been identified that would suggest MS as the etiology for epilepsy in the absence of clinical or radiological evidence that suggests the disease.

Periodic Lateralized Epileptiform Discharges (PLEDs) are seen in a variety of disorders, including in association with MS exacerbations.[54–56] These have been associated with clinical manifestations of altered consciousness or prolonged aphasia, resulting from prolonged complex[54,55] and simple [41] partial *status epilepticus* and with focal motor seizures followed by secondarily generalized seizures. [56]

Magnetic Resonance Imaging (MRI)

Few studies have reported MRI data in MS patients with seizures, and most existing reports do not include systematically acquired imaging data. Even the timing of MRI relative to seizure varies substantially from days to several years within some studies. The multifocal nature of MS, with lesions disseminated in both space and time, complicates attempts to correlate individual lesions with epileptogenesis. Further, pathological series have demonstrated that MS lesions, particularly cortical lesions, seen on pathological examination are frequently not identified on MRI. [40,57,58] MRI data available from several studies is summarized in Table 4.

One investigation specifically sought to examine the relationship between cortical lesions visualized on MRI and epilepsy in MS patients through the use of a double inversion-recovery MRI sequence. MRI in 20 MS patients with epilepsy were compared with MRI in 80 MS patients who did not have seizures. Quantitative measurements showed no statistically significant difference in overall lesion burden between the two groups but reported a statistically significant increase in the presence of cortical lesions (90% versus 48%), a five-fold increase in number of cortical lesions and a six-fold larger volume of cortical lesions in the MS patients with epilepsy.[59] The authors reported no correlation between the detected cortical MRI lesions and presumed seizure origin but hypothesized that this was due to the large number of regions in which lesions were detected and to the variable timing of MRI in relation to seizure. This observation provides an important clue about the mechanism of seizures in MS.

Management

There have not been any prospective studies of the tolerability or efficacy of different antiepileptic drugs (AEDs) used to treat seizure in MS. Several retrospective cohorts have included data on medications, but dosage and response to treatment were reported in inconsistent and sometimes crude fashion.[19,25,45–49] Commonly used medications have included oxcarbazepine, carbamazepine, phenobarbital and phenytoin. No studies reported details on how medications were chosen, what dosages were used, or the predefined endpoints to assess response to treatment or to guide changes in medication regimen. In the absence of

these data, the choice of medications should be based upon the type of seizure disorder (partial versus generalized) and on the tolerability of the medication. Patients with MS commonly have other neurologic symptoms, and consideration of side effects in the context of an individual patient's symptoms (e.g. cerebellar dysfunction, cognitive difficulties, etc.) should guide the choice of antiepileptic medication.

Several studies have reported that seizures in MS have a good prognosis. The epidemiologic study conducted by Kinnunen and Wikström reported that epilepsy spontaneously resolved in nearly half (10 of 21) of their patients.[21] Another epidemiologic study reported *status epilepticus* in 4 of 17 (24%) patients,[19] which suggests a worse prognosis than Kinnunen and Wikström reported. Other reports of MS patients presenting with status epilepticus may support this latter finding.[41,44] An investigation of the seizure characteristics of 51 MS patients reported that 3 of 4 patients with simple partial seizures experienced *epilepsia partialis continua*.[45]

Other studies have reported more variable response to treatment with antiepileptic medications and variability in long-term prognosis. Nyquist et al. found that 35 patients (78%) became seizure free with AED treatment, 5 (11%) had recurrent seizures on AED, and 5 (11%) developed intractable epilepsy.[45] In a series of five patients, all became seizure free on a single AED, although the number of previous AEDs tried was not reported and duration of follow-up was variable. [43] The variability among reporting techniques, the lack of a standardized treatment protocol and inadequate data regarding the dosage and adherence to prescribed antiepileptic regimen preclude generalization based upon the reported data. Striano et al. reported variable prognoses among 13 patients.[47] In a study that included 17 MS patients with seizure, 9 (52.9%) continued to have recurrent seizures despite AED treatment, 5 became seizure free within 4 years (29.4%) and 3 had only a solitary unprovoked seizure. [46]

Pathogenesis

The emerging appreciation of cortical pathological processes in MS[60–62] may describe the pathologic substrate of the described clinical entity of "cortical multiple sclerosis," [63,64] and, possibly, of the observed increased rate of seizures in MS.[59] Cortical demyelination is a very common pathological finding.[57,58,60,61] This finding, taken together with the relatively uncommon development of seizures among MS patients, argues that other factors are also important and that our understanding of the clinical and pathological relevance of cortical demyelination is incomplete.

Descriptions of "cortical MS" have generally focused on patients presenting with primarily cognitive and/or behavioral symptoms. "Cerebral MS" descriptions included some patients (8%) with seizures.[65] Although these case series suggest a clinical relevance of the observed cortical and subcortical demyelination, both of these series employed a poorly defined clinical definition of cases, and the relationship to underlying pathology as well as the validity generalization of this observation to MS patients as a whole is limited.

Cortical demyelination has been demonstrated to occur at early stages in the MS disease course, [66] and cortical inflammation and demyelination are increasingly appreciated as imaging techniques advance.[67–70] This finding supports the clinical observation that frequency of seizures does not correlate with length or severity of MS.

Others have suggested that the inflammatory processes associated with MS lesions or the edema associated with active MS lesions may be responsible for seizures in MS patients.[49] As discussed above, MRI evidence of cortical inflammation has been reported to be associated with epilepsy in MS.[59] Although some MRI studies using conventional techniques have

attempted to suggest that active lesions may be associated with regions of epileptogenesis, this is far from proven, and most of the data argue against this conclusion. The variable timing of MRI relative to seizure in the majority of MRI studies of MS patients with seizure offers very little data from which to draw definitive conclusions. Further, structural MRI provides an incomplete assessment of neuronal or neuritic processes that may be active around the time of onset of epilepsy. The best working hypothesis as to the etiology of seizures in MS is that it results from cortical demyelinating lesions with or without inflammation. Epileptogenic neuronal foci could follow the development of cortical demyelination, which might be relatively asymptomatic otherwise.

Conclusions

Despite variability among the studies investigating seizure frequency, incidence and prevalence in MS, these studies taken together do suggest increased seizure incidence in MS cohorts. The magnitude of this increase seems to be between 2-fold to 3-fold above the general age-matched population. This finding is not particularly surprising. Other disease processes causing damage to the brain parenchyma such as stroke,[71] viral encephalitis[72] and Alzheimer's disease[73] are also associated with increased risk of seizure. Although one could argue that these other diseases affect the cerebral cortex more directly, the effects of demyelination and inflammation on the cortex are increasingly recognized as important in MS, and edema associated with acute MS lesions could also cause cortical hyper-excitability.

Clinically, partial seizures, with or without secondary generalization, appear to be more common. Primary generalized epilepsy has also been reported, albeit more rarely. Investigations of the prognosis of epilepsy in MS patients have yielded conflicting results, although most studies report good seizure control on standard AED regimens. Medication side effects might be more commonly experienced in MS patients, due to the concomitant central nervous system disease in addition to epilepsy. Many MS patients are on other centrally acting medications to treat symptoms related to their MS. These may interact with prescribed antiepileptic drugs, may amplify the adverse effects of these medications and some may increase the risk of seizures in MS patients. The long-term prognosis of epilepsy in MS relative to epilepsy in the absence of MS is uncertain, as is the optimal choice of AED. Future studies may provide insight into these important clinical questions.

Attempts to relate seizures to clinical MS attacks, pathological findings and MRI metrics all reveal our incomplete understanding of the disease mechanisms in MS. Cortical demyelination and inflammation provide attractive possibilities for pathological substrates, although these raise as many questions as answers. Evidence from the available incidence studies suggests that seizures more commonly manifest early in the MS disease course. Some patients report seizure prior to the clinical onset of MS, and many others report seizure within five years of MS onset. Inflammatory processes of MS are more common early in the MS disease course, and this suggests a possible relationship between MS and seizures. As researchers refine and implement MRI techniques relevant to pathological processes important in MS, studies attempting to relate MRI metrics and seizure may become more fruitful.

Seizure incidence has not been reported in the clinical trials of interferon medications or glatiramer acetate. This is unfortunate on several accounts. First, several large clinical trials have enrolled large numbers of well-characterized MS patients from numerous countries that have been followed longitudinally for more than 10 years. Analysis of the placebo arms of these studies would provide a unique opportunity to estimate the incidence and prevalence of epilepsy in MS. Further, since exacerbations are tracked as important endpoints in these studies, investigation of the relationship between exacerbations and seizures could be established or refuted, which might provide a clue regarding the pathogenesis of seizure in MS. Lastly, these

clinical trials have demonstrated that disease-modifying treatments reduce exacerbation frequency in relapsing-remitting MS. If seizures are related to exacerbations, one would expect a reduction in the incidence and prevalence of seizure in the active treatment arms of these trials.

Given that seizures apparently occur more commonly in MS patients than in the general population, physicians should remain alert to this possibility of seizures in their MS patients and manage them accordingly. The optimum choice of medication, duration of treatment and prognosis remain unclear, as does the relationship of these seizures to the disease processes underlying MS.

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 Table 1

 Estimated prevalence of seizures in multiple sclerosis – population-based cohort studies

Location	Number of subjects	Number with seizure	Prevalence (Incidence)	Number of subjects Number with seizure Prevalence (Incidence) MS duration prior to seizure mean \pm SD Reference	Reference
Uusimaa, Finland	599	21	3.5% $\dot{\tau}$	6.45 ± 7.4 years	[21]
Hordaland, Norway	423	17	4.0%	7.4 ± 6.3 years	[19]
Iceland	188		2.3% (SIR=3.0)	5.0 ± 4.1 years	[24]
Rochester, MN	208	5	2.4% (SIR=1.3) $^{\uparrow\uparrow}$	9.6 ± 4.5 years	[23]
Gothenburg, Sweden	255	20	3.5% (SIR=7.8)	*	[20]
Catania, Italy	170	4	2.4% (SIR=3.3)	6.25 ± 6.45 years	[22]

SIR = Standardized incidence ratio

* Data not available \dot{r} SIR not calculated, reported prevalence was estimated to be 4-fold greater than the general population.

⁷⁷Age-adjusted incidence of seizure during the lifetime of patients with MS estimated to be 82/100,000; age-adjusted incidence in the general population of Rochester, Minnesota, 61/100,000.

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Table 2

Estimated prevalence of seizures in multiple sclerosis - hospital-based series

Location	Number of subjects	Number with seizure	Prevalence	Reference
Germany	450	8	1.8%	[74]
Germany	330	14	4.2%	[75]
Italy All MS (definite MS)	2353 (1,459)	40 (34)	$1.7\%~(2.3\%)^{\dagger}$	[48]
Dijon, France	402	17	4.25%	[46]
Belgrade, Yugoslavia	268	20	7.5%	[25]
Naples, Italy	270	13	4.8%	[47]
Catanzaro, Italy	350	16	4.6%	[43]

* Data not available

 † Substantially higher than estimated prevalence rates in Italian cohorts of 0.52–0.62%[18,76]

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Table 3

EEG data

Number of MS patients with seizure	Focal or generalized slowing	Focal or generalized epileptiform changes	Normal	Reference
51	19 (44.2%)	15 (29.4%)	11 (25.6%)	[45]
13	12 (92.3%)	5 (38.4%)	0	[47]
17*	5 (29.4%)	9 (52.9%)	2 (11.8%)	[46]
40	15 (37.5%)	11 (27.5%)	14 (35%)	[48]
21	10 (47.6%)	12 (57.1%)	2 (9.5%)	[21]
6	3 (50%)	3 (50%)	0	[49]
20	12 (60%)	NR	8 (40%)	[59]

*PLEDs 1 (5.9%)

MRI data

Table 4

Number of MS patients with New and/or Gd (+) seizure	New and/or Gd (+) lesions	lesions Evidence of cortical or subcortical lesion	Lesion in region of presumed epileptogenesis	No suspected epileptogenic lesion Reference	Reference
12	NR	3 (25%)	NR	NR	[48]
7	6 (85.7%)	7 (100%)	4 (57.1%)	3 (42.9%)	[49]
17	5 (29.4%)	5 (29.4%)*	NR	*	[46]
20	10(50%)	9 (45%)	<i>†</i>	NR	[25]
5	$3(60\%)^{**}$	5 (100%)	5 (100%)	0	[43]
20	NR	18 (90%)	NR	NR	[65]
NR = Not reported					

NK = Not reported

* In Table 2 of this paper,[46] five subjects were noted to have subcortical plaques and in the discussion section, the authors make the comment "All our patients had clear subcortical involvement," without further clarification.

** Gd enhancement

 $\stackrel{f}{\tau} No$ correlation between lesion and presumed seizure focus