

Epilepsy and multiple sclerosis

Christine Lebrun

Service de Neurologie, Hôpital Pasteur, Nice, France

ABSTRACT – Epilepsy is three to six times more frequent in multiple sclerosis than in the general adult population. The probable anatomic basis for the seizures is areas of inflammation and demyelination in the cortex and juxtacortical white matter. Partial epilepsies with focal seizures often with atypical symptoms and with or without secondary generalisation are the usual pattern. Seizures can be observed as the first symptom of multiple sclerosis, or during relapses, with a direct correlation between paroxysmal phenomena and plaques demonstrated by brain MRI. Infrequently, it can start during the progressive phase, without active inflammation, generally associated with brain atrophy and high lesion load. Generally, the prognosis of epilepsy in multiple sclerosis patients is estimated to be good, without special recommendations or consensus for the choice of anti-epileptic drug. Non-epileptic paroxysmal symptoms may be confused with epileptic seizures. It usually responds to many different antiepileptic drugs.

Key words: epilepsy, multiple sclerosis, prevalence, magnetic resonance imaging, non-epileptic seizures

Epilepsy concerns 0.5 to 1% of the general population (Sanders and Shorvon 1996), but publications concerning its occurrence during the course of central nervous system (CNS) inflammatory disorders are rare. For the clinician, however, its presence constitutes an indication of severity, to be considered in disease management. Thanks to the development of MRI techniques, of new anti-epileptic drugs, and of specific immunosuppressive treatments administered early in the course of CNS inflammatory diseases therapy, onset and evolution of epilepsy have become less prejudicial.

Epidemiology

Multiple sclerosis (MS) is the most frequent primary, chronic inflammatory disease of the CNS in adults; the question of whether epilepsy is more frequent in MS patients has long been subject of debate. Today, we know

that patients with MS have a 14 times higher average risk (between three and 20 based on series 3, 4, 5) of having epileptic seizures, with an incidence that varies between one and 11% depending on the series (Spatt *et al.*, 2001). Coincidental association of the two pathologies is possible, and prevalence in that case is the same as that in the general population.

In epileptic patients, age at onset of MS is identical to that in other MS patients (between 19 and 50 years, the average age being 32). One of the first available studies (Drake and Macrae 1961) reported epilepsy in 4.5% of patients treated for MS, a prevalence confirmed more recently by EEG and MRI findings (Kinnunen and Wikstrom 1986). In MS patients with evolution by flare-ups, incidence of seizures is age dependant, with a frequency 20 times higher between 25 and 40 years.

Depending on the series, reported prevalence is between 3 and 6% (Olafsson *et al.*, 1999, Moreau *et al.*;

Correspondence:

C. Lebrun
Service de neurologie,
Hôpital Pasteur,
30 voie romaine,
06002 Nice,
France
<courriellebrun.c@chu-nice.fr>

1998, Kinnunen and Wikstrom 1986, Boudin *et al.*, 1965), with onset of epileptic seizures 4 to 7 years following MS diagnosis (Cendrowski and Majko'ski 1972); both sex being equally affected.

It is interesting to note that data in the literature is most often retrospective and remains very heterogeneous, with patients having different forms of MS and presenting epileptic and non-epileptic events.

In 12% of cases, epilepsy reveals the MS. In these cases of early and frequently partial epilepsy, epileptic phenomena are not a criterion for initial severity of the MS.

In most cases, a diagnosis of inflammatory disease is made on brain MRI performed as part of the initial work-up following a first seizure. More rarely, MS is diagnosed in the following months, after a second flare-up. Rapid occurrence of a second flare-up characterizes these forms of MS as active, given the short interval between the first 2 demyelinating events.

More rarely, a seizure occurs independently of flare-ups or of handicap progression and the search for contributing factors (*i.e.* associated treatments) is essential in this setting.

Frequency of seizures generally depends on the form of MS, and is correlated with frequency of flare-ups, except in very advanced stages of the disease (between five to less than one per year, depending on whether MS is relapsing-remitting, progressive-relapsing or primary-progressive (Ghezzi *et al.* 1990).

Seizures

Epileptic seizures associated with MS are, in 67% of cases, simple partial motor seizures with or without Jacksonian progression (Drake and Macrae 1961, Olafsson *et al.*, 1999, Moreau *et al.*, 1998, Kinnunen and Wikstrom 1986, Boudin *et al.*, 1965). Secondary generalization is observed in 11 to 50% of cases (Sokic *et al.*, 2001). All forms of epilepsy are possible, given the anatomical diversity of demyelinating lesions. More rarely, cases of *epilepsia partialis continua* (Hess and Sethi 1990, Striano *et al.*, 2003), dysphasic seizures (Spatt *et al.* 1994), myoclonic seizures, musicogenic seizures (Newman and Saunders 1980), dyschromatopsic seizures (Cendrowski, 1990) temporal or generalized status epilepticus (Gambarella *et al.*, 2003, Boudouresque *et al.*, 1980) have been described in MS patients. 10% of seizures remain unclassified (Nyquist *et al.*, 2001).

Physiopathology and radiological findings

Like in most symptomatic epilepsies, pathophysiological findings depend largely on the anatomical location of the lesion. Direct involvement of plaques was proven by anatomopathological studies (Boudin *et al.*, 1965,

Brownell and Hugues 1962) showing cortical or juxtacortical demyelination plaques, and by MRIs showing plaque at all stages of evolution (new plaque with edema, or old plaque with cicatricial gliosis) (Cendrowski and Majko'ski 1972, Kidd *et al.*, 1999, Kermode *et al.*, 1990). A causal relationship was shown to exist between the number, location, size and volume changes of cortical and juxtacortical lesions and onset of epilepsy (Nyquist *et al.*, 2001, Kidd *et al.*, 1999), resulting in a precise clinical seizures classification. Identification of juxtacortical lesions (*figure 1*) at MRI has now been added to the Barkhof diagnostic criteria (Barkhof *et al.*, 1997), increasing MRI sensitivity and precision when making a diagnosis of MS.

The most relevant sequences for identifying potentially epileptogenic lesions are T2 FLAIR, T2 proton density and T1 with gadolinium injection (Moreau *et al.*, 1998, Kidd *et al.*, 1999, Thompson *et al.*, 1993). There is no correlation between total lesions load and the onset of epilepsy.

Exceptionally, a pseudotumoral demyelinating lesion proves to be at the origin of the seizures (*figure 2*). Bilateral frontal atrophy (Moreau *et al.*, 1998), and extensive frontal lesions load on T2 weighted sequences are present in 77% of cases of secondary progressive MS with epilepsy as opposed to 23% in those patients without epilepsy.

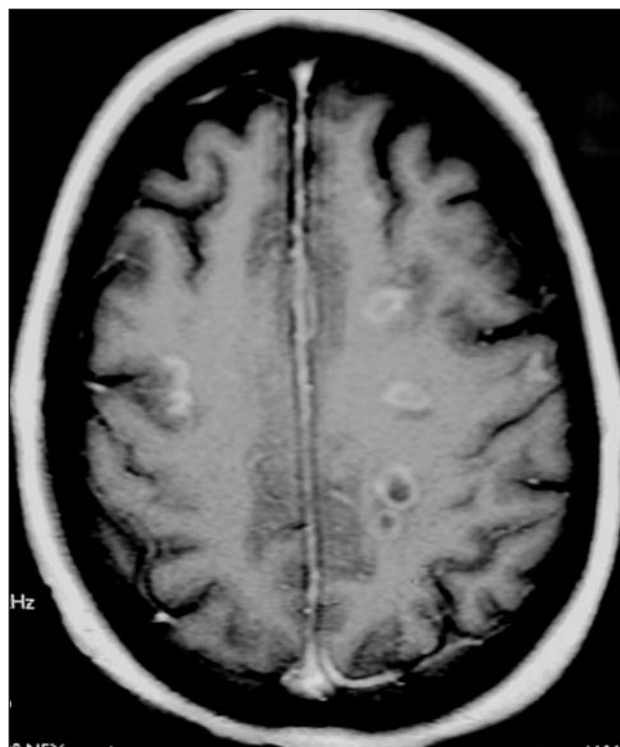


Figure 1. Brain MRI. Axial T1 weighted image with gadolinium injection revealing numerous active juxtacortical lesions.

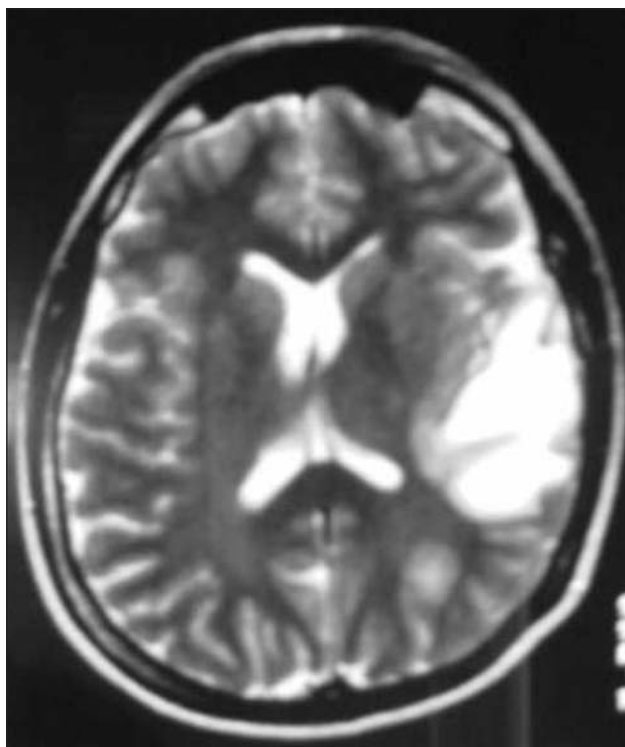


Figure 2. Brain MRI. Axial T2 weighted FSE image showing a left temporo-insular, hyperintense, pseudo-tumoral demyelinating lesion.

Electroencephalographic findings

An electroencephalogram can contribute to the diagnosis and is abnormal in 75 to 85% of cases, showing a slow background with focal or diffuse spike waves (Cendrowski and Majko'ski 1972, Cendrowski, 1990, Boudouresque *et al.*, 1980, Nyquist *et al.*, 2001), findings that are very labile in time and in space and are not always specific. The EEG is normal in only 11 to 25% of cases. In 23% of new cortical lesions (41% of which being frontal) (Moreau *et al.*, 1998), there is a good correlation between focal EEG abnormalities and MRI findings. In 20% of cases, active infraclinical lesions may present with EEG focal spike-waves discharge or with periodic lateralized epileptiform discharges (PLEDS). In 80% of cases of relapsing-remitting MS, seizures and their corresponding electroencephalographic abnormalities are related to disease flare-up (Gandelman-Marton *et al.*, 2003). In a certain number of cases that can be as high as 18% depending on the series, EEG performed in a totally symptom-free context reveals evidence of electrical status epilepticus.

Differential diagnoses of epileptic seizures

Non epileptic paroxysmal events, much more frequent than epileptic seizures, constitute the main differential

diagnosis (Spatt *et al.*, 2001). They occur in 17% of MS patients and take various forms:

Trigeminal, occipital or retroarticular neuralgia; SUNCT, tonic or dystonic movements, cortex related events (*i.e.* sensory symptoms, aphasia, alexia, agraphia, palinopsia, akinesia, paroxysmal pruritus, chorea etc.).

They are usually brief, stereotyped, sometimes occurring several times a day over several days, and then stopping for several months. They are never associated with clonic movements or with altered consciousness. They are sometimes triggered by a sensory stimulus or a voluntary movement. These paroxysmal events, usually the result of myelin and axonal damage, are generally well controlled with antiepileptic drugs at lower doses than those used in epilepsy.

Treatment

Considering that seizures are symptomatic of the underlying active demyelinating plaque, it is primarily recommended to treat the active inflammatory process with high doses of steroids (Ghezzi *et al.*, 1990, Sokic *et al.*, 2001). Ultimate association with an antiepileptic drug is only recommended in case of relapse. Choice of antiepileptic medication is not specific to MS patients (Spatt *et al.*, 2001). It should take into account possible drug to drug

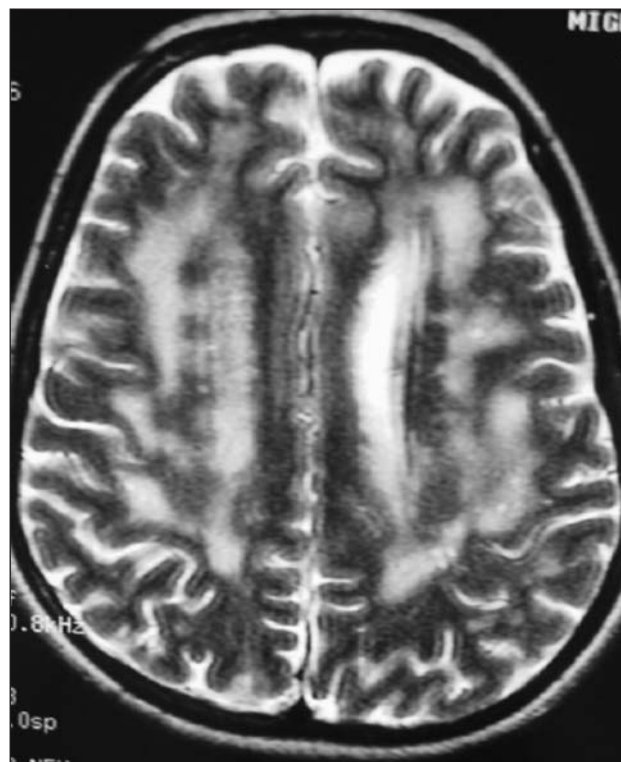


Figure 3. Brain MRI. Axial T2 FSE sequence in a patient with secondary progressive MS revealing confluent hypersignal lesions.

interactions (i.e. with interferon beta, other antiepileptic drugs prescribed previously as analgesics, antispasmodics etc.).

If we are considering epileptic seizures as being a sign of disease activity, brain MRI performed in this setting may reveal cortical or juxtacortical contrast enhancing lesions (Thompson *et al.*, 1993).

Chronic epilepsies necessitating long term antiepileptic treatment, may occur in advanced stages of the disease, are associated with high lesions load on MRI and are not related to relapses (figure 3). Except in very rare cases, multiple sclerosis constitutes a contraindication for epilepsy surgery. There is a case report of successful surgery for a chronic demyelinating lesion presenting with a pharmacoresistant temporal lobe epilepsy (Smith and Elisevich 1998).

Chronic epilepsy associated with cognitive deterioration and serious handicap, can be complicated by status epilepticus and is having a poor prognosis (Nyquist *et al.*, 2001, Poser and Brinar 2003). □

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