Multiple sclerosis (MS) has been increasingly recognized as a risk factor for developing epilepsy by numerous population-based epidemiological surveys. The occurrence of seizures in patients with MS, indeed, is substantially higher than that in the general population, with an overall incidence of about 4%, ranging from 1 to 10.8%. In most MS patients who also develop epilepsy, seizures are chronic, unrelated to any detectable activity of the disease, and are sometimes the first clinical symptom of MS. Otherwise, seizures represent the sole manifestation of relapse in MS.

Despite all these reports, conflicting data exist regarding whether or not the occurrence of epilepsy is associated with a more severe clinical course and prognosis of MS. Thus, some authors reported a higher number of relapses or a more severe course of MS in those patients with epilepsy, while others claimed that MS patients with epilepsy did not have a more severe progression. Moreover, although seizures are typically partial in MS, there seems to be a great variability with regard to the type of seizures and their frequency.

Here we report on five patients with MS who had a highly homogeneous clinical picture characterized by temporal lobe epileptic seizures as the unique manifestation of their disease. An ABSTRACT: Objective: To report on five patients with temporal lobe epilepsy (TLE) as the unique manifestation of multiple sclerosis (MS). Methods: Among 350 consecutive MS patients, we identified 16/350 (4.6%) who also had epileptic seizures. Here, we review their electrophysiological and clinical features. Results: Five of these 16 patients (four female, one male; mean age 34.2 years; range 31 to 38) with MS and epileptic seizures had an extremely homogeneous clinical picture characterized by TLE as the unique manifestation of MS, even at long follow-up (mean: five years; range 4 to 10). In all patients, seizures started in the second or third decade. Brain MRI revealed at least one juxta-cortical lesion within the temporal region. Antiepileptic medication was always effective. Conclusions: The present study provides the first evidence of a peculiar form of MS characterized by TLE as the unique manifestation of the disease with no disability or MS relapses at long-term follow-up.

RÉSUMÉ: Épilepsie temporale comme seule manifestation de la sclérose en plaques. Objectif: Rapporter les cas de cinq patients présentant une épilepsie temporale (ÉT) comme seule manifestation de la sclérose en plaques (SEP). Méthodes: Nous avons identifié 16 patients parmi 350 patients consécutifs (4,6%) atteints de SEP qui présentaient également des crises d’épilepsie. Nous avons revu leurs caractéristiques électro-cliniques. Résultats: Cinq de ces 16 patients, quatre femmes et un homme, dont l’âge moyen était de 34,2 ans (écart de 31 à 38 ans), atteints de SEP et présentant des crises d’épilepsie avaient un tableau clinique extrêmement homogène caractérisé par une ÉT comme manifestation isolée de la SEP, même après un suivi à long terme (moyenne de cinq ans, écart de 4 à 10 ans). Chez tous les patients, les crises avaient commencé dans la deuxième ou troisième décennie. L’IRM du cerveau montrait au moins une lésion juxta-corticale dans la région temporaire. La médication antépileptique était efficace dans tous les cas. Conclusions: Cette étude est la première à rapporter une forme inusitée de SEP caractérisée par une ÉT comme manifestation isolée de la maladie, sans invalidité ou récidive de la SEP au suivi à long terme.

additional striking feature was the very mild course of MS, as none of these patients exhibited any disability or developed MS relapses at long-term follow-up.

**Patients and Methods**

Patients were identified among 350 consecutive patients with a diagnosis of definite or probable MS seen at our Institute in the last 10 years. All MS patients underwent brain magnetic resonance imaging (MRI) study with and without gadopentetate dimeglumine (Gd-DTPA) as part of routine evaluation in subjects with suspected MS. A detailed description of the MRI protocol used at our institution in patients with MS has been previously reported.11

Sixteen of these 350 (4.6%) MS patients had seizures in the course of their illness. In all 16, a detailed history of the type and frequency of seizures was obtained from patients, parents and other relatives at the time of investigation and from a review of the patients’ medical records. All patients had extensive electroencephalographic investigation consisting of repeat EEG recordings with anterior temporal and scalp electrodes, using the 10-20 system for electrode placement. Following this comprehensive clinical, neuropsychological and electroencephalographic evaluation, seizures were classified according to the criteria of the International League Against Epilepsy.12

Four out of 16 patients had an electro-clinical picture of extratemporal epilepsy with partial motor and secondarily generalized seizures and displayed varying degrees of disability as assessed by the Kurtzke Expanded Disability Status Scale (EDSS).13 In an additional two out of 16 patients, transitory partial motor seizures coincided with a clinical relapse. In another two patients with generalized seizures, we considered the possibility that these seizures were related to other causes. In one MS patient, focal epileptic myoclonus occurred in the context of severe MS with progressive motor and cognitive deterioration. In one patient, the diagnosis of epilepsy was uncertain as she had psychiatric disturbances and complained of rare vegetative auras. She also refused to undergo cerebrospinal fluid examination. Another MS patient with epilepsy was excluded because she had had a severe closed head trauma prior to the onset of seizures.

The remaining five of these 16 (31%) patients (four women, one man; mean age 34.2 years; range 31 to 38) with MS and epileptic seizures had an extremely homogeneous clinical picture characterized by temporal lobe epilepsy (TLE) as the unique manifestation of MS. These five patients with MS and TLE are reported in detail in the present paper. In all of them, epileptic seizures were the reason to seek medical advice, and the diagnosis of MS was suggested only by MRI study. All five patients had repeated clinical examinations every 3–12 months with a mean follow-up of five years (range 3–10 years). Disability status was assessed with the use of the Extended Disability Status Scale (EDSS).13 As part of routine evaluation in MS, cerebrospinal fluid examination was also performed in all patients. All of them also underwent visual, somatosensory and acoustic evoked potential study, and also had at least a second MRI approximately one year later. Magnetic resonance imaging was performed on a 0.5 T system at base line and on 1.5-T scanner (General Electrics Signa, Milwaukee) at one year, and included images of the brain and of the cervical spinal cord both before and after IV injection of gadolinium.14

**Results**

The main clinical data of these five patients with MS and TLE are summarized in Table 1. EEG and MRI findings are reported in Table 2. Neurological examination was unremarkable in all five patients and remained unchanged in the four to 10-year follow-up. Memory function was normal at base line and follow-up. Visual, somatosensory and acoustic evoked potential were normal in all patients. Hematological and biochemical investigations, vitamin B12, serum folate, vitamin E levels, very long chain fatty acids, and arilsulfatase-A levels were always normal. An autoantibody screen including anti-nuclear, anti-DNA, anti-mitochondrial, anti-microsomal, anti-endomyosal, and anti-gliadin, was negative. The coagulable profile including activated partial-thromboplastin time, fibrinogen, antithrombin III, protein C activity, protein C antigen and protein S total antigen was always normal. In all patients but one (patient 1), cerebrospinal fluid analysis by isoelectric focusing revealed the presence of oligoclonal IgG bands. Based on Poser committee diagnostic criteria for MS,10 one patient (patient 1) had a clinically definite MS as she had, prior to the onset of seizures, an acute unilateral optic neuritis. The remaining four patients had a laboratory-supported definite MS (category B3). Moreover, all our patients fulfilled the MRI spatial diagnostic criteria for MS that have recently been promulgated, especially for patients with a clinically isolated syndrome.14 Indeed, all had at least nine deep white matter hyperintense lesions in both hemispheres, of which at least three were periventricular (see Table 2). Moreover, utilizing the criteria proposed by the CHAMPS study group to make an early diagnosis of MS,15 the combined clinical, laboratory and MRI findings indicate that our patients indeed have MS.

Importantly, all patients had at least one juxta-cortical lesion in the temporal region that coincided with the epileptogenic region as assessed by detailed electro-clinical investigation (Figure 1 and 2). At base line, in three of five patients (1, 3 and 5) the juxta-cortical lesion in the temporal region showed some enhancement after Gd-DTPA, which disappeared at follow-up. Nonetheless, these temporal lesions were still recognizable in all of them. It should be noted that a few new lesions were seen only in patient 3 at follow-up.

Regardless of the epileptic disorder, no additional identifiable etiologic factors were found in any patients. Two of them (patients 1 and 2) had a positive family history of simple febrile convulsions. The habitual seizures started in the second or third decade in all patients (Table 1). At the beginning of their epilepsy, four out of five patients (1, 3, 4 and 5) had simple partial seizures alone, which continued to be the only type of seizure for several months. Thereafter, three of these four patients also experienced complex partial seizures or very rare secondarily generalized seizures. In all patients, simple partial seizures were characterized by rising epigastric sensation associated with mild confusion and other vegetative phenomena. Three patients (1, 2 and 3) also had psychic and emotional phenomena such as fear, forced thinking or complex visual hallucinations. Patient 5 experienced olfactory hallucinations.
Table 1: Five patients with temporal lobe epilepsy and multiple sclerosis: clinical data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset of epilepsy (yrs)</th>
<th>Sex, Age (yrs)</th>
<th>Seizures types (frequency)</th>
<th>Antiepileptic drug (dosage/day)</th>
<th>Outcome (follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>woman, 37</td>
<td>affective, vegetative, CP (weekly)</td>
<td>Carbamazepine (800 mg)</td>
<td>seizure free (10 years)</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>woman, 38</td>
<td>affective, vegetative, CP (monthly)</td>
<td>Valproate (1.0 gr)</td>
<td>seizure free (8 years)</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>woman, 34</td>
<td>vegetative, affective, CP (monthly)</td>
<td>Carbamazepine (800 mg)</td>
<td>seizure free (5 years)</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>woman, 32</td>
<td>Auditive, vegetative, CP, sG (weekly)</td>
<td>Clobazam (20 mg)</td>
<td>seizure free (5 years)</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>man, 31</td>
<td>Olfactive, vegetative, CP, sG (every 3 months)</td>
<td>Oxcarbazepine (800 mg)</td>
<td>seizure free (4 years)</td>
</tr>
</tbody>
</table>

CP = complex partial; sG = secondarily generalized tonic-clonic

Table 2: Five patients with temporal lobe epilepsy and multiple sclerosis: interictal EEG findings, and sites and appearances of baseline MR abnormalities

<table>
<thead>
<tr>
<th>Patient</th>
<th>Interictal EEG findings</th>
<th>Juxtacortical</th>
<th>Periventricular</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right temporal sharp wave complexes</td>
<td>one* in right temporal region</td>
<td>four</td>
<td>three</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>one in left temporal limbic region</td>
<td>six</td>
<td>four</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>one* in right temporal limbic region</td>
<td>five</td>
<td>five</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>one in left limbic temporal region</td>
<td>seven</td>
<td>two</td>
</tr>
<tr>
<td>5</td>
<td>Left</td>
<td>two* in left anterior temporal region</td>
<td>nine</td>
<td>three</td>
</tr>
</tbody>
</table>

* enhanced after gadolinium.

Figure 1: EEG and brain MRI study in patient 2. Note spiking activity involving the left temporal region on EEG recording (A), which coincided with the juxta-cortical lesion within the left temporal lobe depicted by T2-weight coronal MR images of the brain (B).
Complex partial seizures were almost always preceded by simple partial seizures and typically consisted of behavioural arrest or staring with or without automatisms, followed by dystonic posturing and occasionally by slow slumping to the floor. None of the patients experienced prolonged (more than 20 minutes) postictal confusion.

On EEG, interictal sharp-slow wave complexes or rhythmic delta waves occurred mainly during drowsiness or nonREM sleep, and always involved one temporal region (Figure 1 and 2). In all patients, concordance of data indicated a strictly unilateral temporal origin of the seizures, from the dominant left hemisphere in three, and from the right temporal region in the other two patients. Antiepileptic medication was effective in all treated patients. An attempt to discontinue anticonvulsant therapy in patients 1, 2 and 3 induced recurrence of habitual seizures. The therapy was restarted and none of them had any further seizures.

DISCUSSION

The course of disease in MS is highly variable with a wide range of disability and rates of progression, and the mildest form of MS that is clinically apparent has been labeled benign MS.\(^\text{16}\) It has been claimed that the milder forms of MS typically present with optic neuritis or sensory symptoms.\(^\text{17}\) For the first time, we have illustrated that MS may present as epilepsy alone, and the latter may constitute the unique manifestation for many years. In each of our patients MS was diagnosed only after the onset of epilepsy, which remained the main clinical manifestation in the following years. Most important, the fact that the EDSS score was unchanged and none of our patients developed an MS relapse at long-term follow-up strongly indicates that this is a benign variant of MS with a very mild course. There is now good evidence, indeed, that clinical features in the first two to five years after the development of a clinically isolated syndrome are a useful indicator of prognosis and a reliable predictor of long-term disability in patients with MS.\(^\text{18,20}\)

Specifically, the frequency of relapse and the interval between relapses during the first two years,\(^\text{18}\) incomplete recovery from relapses during the first five years,\(^\text{19}\) and the degree of disability after five years\(^\text{20}\) have been associated with the development of disability up to 25 years later.

Several studies have already demonstrated that patients with MS have a threefold risk of developing epilepsy, and epileptic seizures may also be the first clinical manifestation of MS, ranging in frequency from 11 to 45% of patients with MS and seizures.\(^\text{3,6,7,9,21}\) In all these cases, as in our patients, epilepsy is treatable even if it may be occasionally medically intractable,\(^\text{22}\) and seizures usually start in the second or third decade of life. Before this study, however, no one clearly addressed the issue that epilepsy may constitute the unique manifestation of MS for many years. In all our patients, in fact, partial epileptic seizures were the reason to seek medical advice, and the diagnosis of MS was suggested mainly by MRI study, which always revealed a chronic demyelinating lesion involving either temporal region. Thus, our findings of MS presenting as TLE further support the notion that the diagnosis of MS should be considered in patients with partial epilepsy starting in adulthood. Nonetheless, we are not aware of any definite explanation for the favorable outcome of MS in our patients. Since all but one of the patients we report on were women and, because there is evidence that women are about twice as likely to follow a milder course as men,\(^\text{19}\) gender could be considered an influential factor.

Moreover, one could question if epilepsy is not just a

\[\text{Figure 2: EEG and brain MR study in patient 4. Also in this patient, slow delta waves intermingled with sparse sharp-slow complexes occurred over the left temporal region (A), where T2-weight MRI scan of the brain depicted subcortical demyelinating lesions (B).}\]
coincidence in our patients. We believe that the strict concordance of the electro-clinical findings with the juxta-cortical plaque within either temporal lobe strongly supports a causal connection between MS and TLE in our patients. A previous electro-clinical and neuropathologic study definitively illustrated that a chronic unremitting demyelinating plaque situated in the temporal region at the junction of gray and white matter may be itself epileptogenic.22 Also the fact that MS lesions may often arise within the juxta-cortical white matter and cortex is not surprising, as it was recently demonstrated by a postmortem neuropathologic study in patients with MS.23 Accordingly, there is now good evidence that cortical lesions are probably of much greater importance than previously thought and contribute to neurological dysfunction in patients with MS.24

Finally, given that in three patients the occurrence of seizures coincided with an active juxta-cortical temporal lesion on brain MRI, one could argue that at least in these three patients seizures were an acute, direct consequence of new MS lesion formation, rather than reflecting a chronic epileptic disorder and thus, there would have been no need for treatment. The subsequent course in two of these patients, however, whose seizures recurred after antiepileptic discontinuation, favors much more the latter hypothesis that seizures were related to the effect of chronic juxta-cortical MS plaque, which was still detectable on brain MRI study.

REFERENCES