Prevalence of epilepsy in a case series of multiple sclerosis patients

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ABSTRACT
Objective: The prevalence of epilepsy in multiple sclerosis (MS) patients has been a subject of interest for some years. The objectives of this study were to describe the clinical, radiological and electroencephalographic characteristics of epileptic seizures and to calculate the prevalence of epilepsy in a case series of MS patients. Method: Medical charts of MS patients were reviewed and patients who had suffered epileptic seizures were identified. Results: Of 160 cases analyzed, 5 had suffered epileptic seizures and one had comorbid mesial hippocampal sclerosis, confirmed by magnetic resonance imaging in a patient with complex partial seizures that began fifteen years prior to her diagnosis of MS. In the other four patients, seizures occurred both during the acute phase of the disease and in the chronic phase. Conclusion: The prevalence of epileptic seizures in MS patients in this study was 2.5%, similar to that found in other studies. Key words: multiple sclerosis, epilepsy, prevalence, epileptic seizure.

Prevalência de epilepsia numa coorte de pacientes com esclerose múltipla

RESUMO
Objetivo: A prevalência da epilepsia em pacientes com esclerose múltipla (EM) tem sido objeto de interesse há vários anos. Os objetivos deste estudo foram descrever as características clínicas, radiológicas e eletroencefalográficas das crises epilépticas e estimar a prevalência de epilepsia na EM numa série de casos. Método: Foram revisados prontuários de pacientes com EM e identificados os casos que apresentaram crise epiléptica. Resultados: Dos 160 casos analisados, cinco apresentaram crise epiléptica, sendo que, um caso, houve a presença de comorbidade com esclerose mesial do hipocampo, comprovada através de ressonância magnética numa paciente com crises parciais complexas iniciadas quinze anos antes do diagnóstico de EM. Nos outros quatro pacientes, as crises ocorreram tanto na fase aguda da doença, como na fase crônica. Conclusão: A prevalência de crises epiléticas nos pacientes com EM neste estudo foi de 2,5%, semelhante à encontrada em outros estudos. Palavras-chave: esclerose múltipla, epilepsia, prevalência, crise epiléptica.

Multiple sclerosis (MS) is a chronic neurological disease that is clinically manifested by a wide spectrum of signs and symptoms that have been organized by Kurtzke¹ in a dysfunction scale that analyzes seven functional systems distributed into pyramidal, sensory, cerebellar, brainstem, visual, bowel and bladder and cerebral functions. An eighth item on this scale is reserved for other, less common neurological manifestations that may be related to the disease, such as epileptic seizures observed during the chronic phase of the disease or, less frequently, as an initial manifestation of the attack.

The prevalence of epilepsy in MS patients has been the focus of study since the beginning of this century; however, the topic remains controversial, since findings have varied from 0.89 to 17% according to
the series studied2-4. There is evidence that patients with MS are at a greater risk of developing epileptic seizures compared to the general population (0.5-1%)2,4.

No studies have yet been carried out on the association between epilepsy and MS in Brazilian patients. Until the 1970s, MS was considered to be very rare, almost nonexistent, in tropical regions of South America where the climate is hot and the population is ethnically diverse. Although epidemiological studies initiated in Brazil in the 1990s confirmed the low prevalence rates of MS (15% in São Paulo and 5% in Rio de Janeiro), they described the clinical profile and course of MS as being similar to the characteristics of the disease found in Caucasian populations in the northern hemisphere where prevalence rates are highest5,6. The objective of this present study was to analyze the frequency and characteristics of epileptic seizures in a cohort of ambulatory patients with MS in the city of Rio de Janeiro (Brazil), correlating clinical data with electroencephalography and neuroimaging findings.

METHOD
A descriptive, cross sectional study was carried out. The research project was approved by the accredited ethics committee of the University Hospital and Gafreê Guinle.

Patients with MS diagnosed according to the criteria defined by McDonald et al.7 and revised by Polman et al.8, with epileptic crises as defined by the International League against Epilepsy (ILAE)9, were selected from SIAPEM10, an electronic database for the evaluation of multiple sclerosis in tropical countries. The database search included all MS patients followed-up between 1997 and 2007 at the private clinic of one of the investigators (RMPA), a specialist in demyelinating diseases in the city of Rio de Janeiro, Brazil. Demographic and clinical data on MS patients were collected: sex, skin color, place of birth, age at first attack, number of attacks, clinical course of the disease in accordance with the consensus on its subtypes drawn up by Lublin and Reingold11: relapsing remitting, secondary progressive, primary progressive or progressive relapsing, duration of the disease at the time of last visit, degree of disability at the last evaluation, analyzed according to the expanded disability status scale (EDSS)1, classification of MS as benign based on an EDSS score of 0-3 over a duration of 10 years of the disease12 and data on epileptic seizures occurring under the following circumstances: prior to the diagnosis of MS, as the only manifestation of the attack or occurring in the chronic phase of the disease. Patients with MS and epilepsy were contacted by one of the investigators (CDV), a specialist in neuropsychology certified by the Brazilian Society of Clinical Neurophysiology, and were invited to participate in the study. After signing the informed consent form, patients were submitted to the research protocol, which included the history of epileptic seizures, review of supplementary tests (electroencephalography [EEG] and magnetic resonance imaging [MRI]), an additional EEG using a 20-channel Nihon Kohden scanner and analyzed by the investigator (CDV), and an additional brain MRI using a 3-T scanner.

RESULTS
Data on 160 MS patients from the SIAPEM10 database were reviewed. One hundred and twenty of these patients (75%) were female and 40 (25%) male. Fifteen (9.3%) were of mixed race and 145 (89.7%) were white. Age at onset of the disease ranged from 16 to 43 years (mean 28.20±9.62 years).

With respect to the clinical course of MS, 133 patients initially had the relapsing remitting form, of which 27 went on to develop the secondary progressive form of the disease. The remaining 10 patients had the primary progressive form, of which 5 had progressive relapsing MS. The neurological evaluation carried out at the last medical consultation after a median of 10 years of the disease (range 1-42 years) showed a median EDSS score of 3 (range 0-8). Of the 94 patients who had had the disease for 10 years or more, 43 had an EDSS score ≤3 corresponding to the benign form of the disease as defined by Weinshenker13. Familial MS was reported by two patients (a sister and a second-degree cousin), neither of whom had a family history of epilepsy.

Epileptic seizures occurred in five patients, four females and one male, all of whom were white. In the four women, the disease developed with a relapsing remitting course, in a benign form, as defined by a mean duration of the disease of 16 years and an incapacity index rated between 0 and 2. The only male patient had the primary progressive form of the disease, evolving with severe incapacity over the long term with the patient confined to a wheelchair at the last consultation, 30 years after onset of the disease.

Clinical-laboratorial correlations
The frequency and temporal relationship of the epileptic seizures with the clinical course of MS and electrographic findings from the intercritical period are shown in Table. EEG findings showed diffuse epileptiform abnormalities (Case 1) or abnormalities located unilaterally or bilaterally in the temporal regions (Cases 2 and 4), diffuse slowing or slowing localized in the temporal regions (Cases 1, 3 and 4), and normal tracing (Case 1).

Serial brain MRI scans were reviewed and all five patients who had had epileptic seizures were found to fulfill the MS radiological criteria defined by Barkhof14 and Tintoré14.
Description of the seizures and MRI correlation

**Case 1** – A 30-year old woman had a complex partial seizure, motor symptoms on her right side, followed by secondary generalization. Investigation by her clinician included a brain computed tomography scan and cerebrospinal fluid evaluation for neurocysticercosis, which was unconfirmed. Four years later she developed paresthesia in her lower limbs, abdomen and hands, and Lhermitte’s sign, together with small demyelinating cervical spine lesions. Complete remission was achieved with corticoid therapy. Three years later, she had a further complex partial seizure. Brain magnetic resonance imaging (MRI) showed a rounded area that was T1-hypointense and T2-hyperintense with perilesional edema, in addition to hyperintense lesions on T2 and FLAIR, localized in the periventricular and subcortical regions of both hemispheres of the brain, left middle cerebellar peduncle and right semiaval center, with contrast uptake. Cervical spine MRI showed a hypersignal on T2 at an intramedullary site at C3. Treatment was initiated with interferon beta-1a and anticonvulsants. At the latest evaluation, the patient remains asymptomatic and MRI showed foci of demyelination with no contrast uptake in the semioval centers, corona radiata and white matter adjacent to the lateral and subcortical ventricles of the frontal-parietal-occipital lobes.

**Case 2** – A 45-year old woman had reversible, unilateral optic neuritis at 29 years of age. One year later the diagnosis of MS was confirmed following complaints of cervical spine pain and paresthesias in upper limbs. MRI showed a hypersignal on T2-weighted images of the posterolateral aspect of the cervical spine at C2 level, in addition to other similar images in the left middle cerebellar peduncle, tegmentum, periventricular white matter, and in the area perpendicular to the corpus callosum. In the ensuing years, she suffered further partially reversible seizures, characterized by central facial palsy and right hemiparesis coinciding with the appearance of new brain MRI lesions. At 37 years of age, she began to have tonic-clonic convulsive seizures that were preceded by simple and complex partial seizures that were difficult to manage but eventually controlled with the use of anticonvulsant polytherapy. At the latest evaluation, the patient had pyramidal syndrome in all four limbs and left crural monopa-
resis. MRI showed a hyperintense signal in the hippocam-
pi and white matter in the temporal lobes as well as mul-
tiple hyperintense areas on T2 and FLAIR images, in the
corpus callosum, callosal-septal interface, periventricular
white matter, semiomial center and corona radiata; with no
contrast uptake. Foci were found in the brainstem, cere-
bellar peduncles and cerebellar hemispheres.

**Case 3** – A 27-year old woman who, in the postpar-
tum, presented medullary syndrome at T10 level, im-
proving spontaneously after a few days. Six years later,
six months after the birth of her second child, she had
another thoracic attack at the same level, remission once
again occurring spontaneously. Cervical and thoracic
MRI showed non-contrast enhancing, hyperintense foci
on T2 in the anterior portion of the bulbus and cervical
spine at C2, as well as in the lateral portion of the thorac-
ic spine at T4-T5. Some months later, optic neuritis de-
veloped on the left side. Brain MRI showed foci of hyper-
intense signal in the periventricular white matter on T2,
frontal lobe, periventricular region, with contrast uptake.
Other attacks occurred in the following years, character-
ized by numbness on one side of the face and tongue, tet-
raparesis and ophthalmoplegia of cranial nerve III. Fif-
ten years after the onset of the attacks, the patient had a
complex partial seizure that began with motor manifesta-
tions in her right upper limb. Brain MRI showed a vo-
luminous pseudotumoral lesion on the left temporal lobe
on T1-weighted image, with annular contrast enhance-
ment and multiple periventricular hyperintense foci with
no contrast enhancement. Her most recent neurological
evaluation was normal and MRI showed hyperintense le-
sions, situated bilaterally in the semiomial center, corona
radiata, in the white matter adjacent to the lateral ventri-
cles, corpus callosum, callosal-septal interface, cerebellar
hemispheres, left middle cerebellar peduncle and right
cerebral peduncle. Reduction in the rounded lesion lo-
cated in the left temporal lobe. Hippocampi slightly re-
duced in volume.

**Case 4** – A 14-year old girl with recurrent complex
partial seizures attributed to emotional problems. At 23
years of age, she began to have seizures again, with sec-
ondary generalization. She was treated with anticonvul-
sants, which controlled the seizures. At 45 years of age,
she complained of diplopia and imbalance; however, a full
recovery was reached following corticoid therapy. Eight
months later, she had another seizure with the same char-
acteristics as the previous ones. Brain MRI was compat-
ible with mesial hippocampal sclerosis. Current neurolog-
ical exam was normal and MRI showed multiple hyperin-
tense, non-contrast enhancing foci in the white matter of
the cerebral hemispheres, periventricular regions, corti-
ical-subcortical regions of the insular, frontal and parietal
lobes on the right, and callosal-septal interface.

**Case 5** – A 27-year old male had a generalized tonic-clonic seizure. Eight years later, he developed para-
resis with slow progressive deterioration, eventually re-
quiring a wheelchair. Brain MRI showed areas that were
T2-hyperintense and T1-hypointense in the periventric-
ular and subinsular white matter, and in the white matter
present in the semiomial centers, internal capsules and
brainstem. It was not possible to carry out a current clin-
ical and radiological evaluation in this case.

**DISCUSSION**

In 1994, Charles M. Poser already alerted the medi-
cal community to the need for greater accuracy in the di-
agnosis of MS for clinical research purposes, emphasizing
the need for a differential diagnosis, established through
clinical evaluation and supplementary testing, with other
idiopathic, demyelinating diseases, particularly acute dis-
seminated encephalomyelitis and optic neuritis. This in-
vestigator affirmed that the correct diagnosis of MS is the
most important pillar of epidemiological studies.

Clinically, the diagnosis of MS requires at least two
attacks to have occurred, indicating that different sites of
the CNS have been affected at different times, i.e. disem-
ination in time and space. The course of the disease varies
individually; however, the natural history of the relapsing-
remitting and primary progressive evolutive forms has al-
ready been defined. The relapsing-remitting form has the
best prognosis but may, however, evolve to the second-
ary progressive form. In the present series, among the MS
patients in whom onset of the disease occurred in the rel-
apsing-remitting form, 57% of those in whom the dura-
tion of the disease was ≥10 years had the benign form.
This characteristic of MS in Brazilian patients has already
been reported in other studies. The primary progres-
sive form occurs in 10-20% of cases and is differentiated
from the other form by affecting both men and women
similarly, by having a later onset and by leading to great-
er incapacity. Confirming these data, the frequency of
the primary progressive form of the disease in this sample
population was 16% and only 1 of the 27 patients had
mild incapacity after 10 years of the disease. The frequen-
cy of 2.9% of familial cases was similar to that found by
Pereira among 640 MS patients enrolled at the Hospital
da Lagoa in Rio de Janeiro, Brazil. As already defined, the
functional systems most affected by MS consist of the py-
ramidal and sensory systems. Epileptic seizures are very
rare and their prevalence in the population of Rio de Ja-
neiro remains to be defined.

Five patients of this series had epileptic seizures; how-
ever, only in four cases (three women and one man) was
it possible to associate the epileptic seizure with the clin-
ical status of MS. The disease progressed in the relapsing-
remitting form and was considered benign in the three
female patients and primary progressive in the male patient, leading to severe incapacity over the mid-term.

The exact prevalence of epileptic seizures in MS patients is a controversial issue when analyzing serial studies. Epilepsy occurs in 0.5 to 1% of the general population. Studies on the relationship between epilepsy and MS have indicated a three to six-fold greater risk of an epileptic seizure in patients with MS compared to the general population.3,19,20

Methodological differences such as patient selection, differences in terminology, diagnostic criteria of MS, definition of epilepsy and a lack of differentiation between event-related seizures and seizures in epilepsy may be responsible for the difference in the prevalence rates reported in the various studies, which vary from 0.89%21 to 17%.1 According to Poser and Brinar22, criticism is justified when the diagnostic criteria for the selection of MS patients are not clear and standardized.

In the present study, if only the clinical data were taken into consideration, the prevalence of epileptic seizures and MS would be 3.1%. However, analysis of serial studies of brain MRI and EEG enabled a causal relationship to be established between the diagnosis of mesial hippocampal sclerosis and partial control of the convulsive crises in one of the patients, leading to a lower prevalence of 2.5%. This result was similar to those found in the studies carried out by Ghezzi et al.2 in Italy, Olafsson et al.19 in Iceland and Nicoletti et al.3 in Sicily, all of which included a greater number of cases.

In the MS patients of this study who had epileptic seizures, various aspects were identified with respect to the clinical data, the varying patterns of the seizures, the occurrence of seizures in the different evolutive phases of the disease and the electroencephalographic and neuroimaging results that are in accordance with data that have been described and discussed in the literature.

With respect to the pattern of the seizures, in the majority of cases the seizure was found to be of the partial type with or without secondary generalization, which is to be expected considering the relationship with the subcortical and juxtacortical inflammatory lesions as shown in the neuroimaging exams.

Chronic epilepsy is presumably unrelated to new attacks of MS but relates rather to the effect of the location of the disease on the cortical plate. According to Lebrun20, epileptic seizures may begin during the chronic phase of MS with no active inflammation and are generally associated with cerebral atrophy and an elevated number of lesions. Case 2, the only patient with recurrent seizures that began 10 years after the first MS attack, fits this model in which brain MRI shows no acute inflammatory activity but a large number of confluent lesions affecting the white brain matter, and cortical atrophy. Serial brain MRI scans, including the scan carried out on the 3-Tesla scanner, showed that the majority of lesions characterized by hyperintense signals were situated in the white matter of the temporal lobes, causing thinning of the hippocampus.

The susceptibility of the hippocampus, amygdala and temporal lobe in triggering epileptic seizures in central inflammatory diseases has been clearly demonstrated in this study. In addition to the patient described above, who had chronic epilepsy associated with lesions to the temporal lobes, the patient in Case 3 had a complex partial seizure with a single manifestation of an acute pseudotumoral MS lesion associated with intense inflammatory activity localized in the temporal lobe. The effect on the temporal lobe in the postcritical period and over the long-term also led to cognitive dysfunction.

In agreement with the data reported by Ghezzi2, no correlation was found between the frequency of epileptic seizures and the severity of MS analyzed using the incapacity index. Even in the patient with the relapsing-remitting form who had a large number of epileptic seizures over a period of one year until initiating continuous use of the appropriate anticonvulsant drug to control the crises, EDSS score was 3 after 29 years of the disease, thereby classifying this patient as having the benign form of MS.

At the time of their epileptic seizures, none of the patients in this study were in use of any drugs that could have triggered the seizures such as methylprednisolone or interferon, although they had used them at some time during their illness.

It is well-known that MS predominantly affects the deep and periventricular white matter; however, demyelinating lesions have also been detected in the juxtacortical region and even inside the cerebral cortex. Brownell and Hughes23 found a total of 1,594 plates in the histopathological exams of 22 patients, of which 80 (5%) were in the cortex and 265 (17%) were at the cortex-white matter junction. The accumulation of cortical and subcortical lesions has been shown to be greater in cases of MS with epilepsy compared to those cases without epilepsy.

Five out of 160 patients had epileptic seizures at some phase of the disease; however, it was only established that the seizure was related to MS in four of these cases, resulting in a prevalence of 2.5%. This study reinforces the need for supplementary MRI investigation in epidemiological studies on MS, since this diagnostic tool is capable of identifying other types of CNS lesions related to the appearance of epileptic seizures, such as mesial hippocampal sclerosis, as shown in one of the cases of this series.

REFERENCES