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EPILEPSY AND MULTIPLE SCLEROSIS: COMORBIDITY OR UNIQUE PATHOLOGY?

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Abstract

Seizures have long been recognized to be part of the disease spectrum of multiple sclerosis (MS). While they occur in only a minority of patients with MS, epileptic seizures can have serious consequences. The treatment of MS can be epileptogenic, and antiepileptic treatment can conversely worsen the symptoms of MS. In this article we present an overview of the current literature on the epidemiology, clinical presentation, pathology, imaging, prognosis and treatment of epileptic seizures in MS.

Key words: Multiple sclerosis, ophthalmologic symptoms

Introduction

The International League Against Epilepsy (ILAE) defines epilepsy a neurological disease caused by one of the following conditions: [1] at least two unprovoked crisis (or reflected) occurred in> 24 h away; [2] a crisis not caused (or reflected) and a probability of further crises similar to the overall risk of recurrence (at least 60%) after two unprovoked crisis, over the next 10 years; [3] diagnosis of an epileptic syndrome. An epileptic seizure is in the occurrence of transient signs and / or symptoms due to abnormal neuronal activity, excessive or synchronous in the brain.

Multiple sclerosis and epilepsy are two chronic conditions of the central nervous system whose comorbidities in the same patient despite being well known still has not been fully understood. The literature over the years has reported conflicting data on the incidence of the disease in epileptic patients with multiple sclerosis as the studies often did not include patients who were already suffering from epilepsy before the onset of MS, but also because the diagnostic criteria of these last are frequently changed over time for the advent of the Rm that has completely changed the diagnostic approach and the search for the two pathological conditions. The literature shows that the risk of epilepsy in patients with multiple sclerosis is 3 to 6 times higher than the healthy population, is more common in young age with peak incidence between 4 and 7 years after the onset of multiple sclerosis and is prevalent in the female sex. The frequency of seizures seems to be related to the number of exacerbations of multiple sclerosis [6] and the seat of injury especially when present in the cortical or iuxtacorticali [7-8] (Figure 1).

Material and Method

Ethiopathogenesis

It is widely reported that focal lesions caused by tumors, abscesses and other situations may be triggering epileptic foci but there are few data indicating the demyelinating lesions of multiple sclerosis as a cause of epilepsy. One possible anatomical substrate for the epileptic pathology in multiple sclerosis consists of areas of inflammation and demyelination in the cortex and white matter justacorticale with reactive gliosis, edema and alterations of enzyme ATP Na-K dependent [21]. The finds show pathologic alterations cortical or subcortical but typically associated with varying degrees of atrophy. It is assumed that the alteration of sodium channels may be a common pathogenetic element in the same patient from the onset of epilepsy and multiple sclerosis [8], when especially when epilepsy precedes the onset of MS.

Clinical and instrumental Issues

Seizures are included in the spectrum of multiple sclerosis symptoms and they may arise in the course of relapse or always be present from which specific antiepileptic treatment. Crises can be partial or generalized, primary or secondary, with the same prevalence of epileptic general population. Partial seizures with or without secondary generalization are the most frequent type. Among the partial seizures focal seizures are twice as frequent complex partial unlike the general population in which this ratio is reversed. They may also be present in partial or generalized crisis. They are present, but more rarely, unusual forms of epilepsy as musicogena or disphasic state [11-12].

It is important to consider that patients with MS during the course of the disease may show clinical symptoms such as paroxysmal epileptic-like spasms, dizziness, diplopia, and more, to differentiate the disease seizure in order to establish the correct clinical diagnosis and therapeutic [12]. Seizures can also be a rare side effect of therapies for multiple sclerosis in particular glatiramer acetate, fampridine, cannabis and derivatives or even more rarely with beta interferon, probably for a lowering of the seizure threshold [10-11].

EEG abnormalities are present in approximately 60% of patients with multiple sclerosis and are generally in relation to the site of injury or over the stage of the disease and the particular type of course. There are no specific EEGgraphic patterns and likely to be indicative of the effects of therapy with DMD or AEDs in particular. Generally it detects the presence of slow theta activity synchronous or asynchronous, focal or generalized, often of reduced voltage. These activities may present more rarely paroxysmal elements faster morphology type single-point or polispike, often unrelated to the clinical picture. More frequently we can observe lability to the hyperpnea with induction during the execution of non-epileptic paroxysmal phenomena such as numbness or spasms. In some patients with focal critical episodes can be observed PLEDS (periodic lateralized epileptiform discharges) [12].

The relationship between the EEG and neuroradiological finding to date have not yet been clearly defined. Presumably in the early stages of disease flare edema present level of demyelinating lesions that may have epileptogenic effects would be reduced with steroid therapy. Multiple sclerosis

presents clinical and neuropathological multifocal and for this reason it is not possible to identify a particular pattern specific to neuroimaging as a cause of epileptic disease. In most cases there is a specific correlation between the lesion topographic demyelinating cortical or subcortical and the clinical manifestation of the crisis but often this element is not detectable to the neuroimaging studies [13-14].

From the literature we observe that the prognosis of the disease epileptic patients with multiple sclerosis is controversial. The first studies in this regard [15] showed a favorable prognosis than the general population, in particular regarding the frequency and to control seizures but then that item is no longer highlighted [16]. Often critical episodes individual or isolated in time require no antiepileptic treatment. However the risk of status epilepticus in patients with late-onset epilepsy and EEG abnormalities recommend the use of specific therapy [23].

Seizures can occur throughout the course of demyelinating disease and they are not related to the particular variant of MS. It is controversial the concept of the relationship between crisis and relapse as it is not yet well established whether an increase in seizure frequency may be a factor aggravating the disease, expression of increased disability, or the transition to the secondary progressive form [17-18].

Conclusion

Therapy

The treatment of epileptic disease in patients with multiple sclerosis does not show specific and different protocols than the general epileptic population. From the literature, we find that you have used all the AEDs available both during the normal course of the disease during relapses during which few reports highlight the improvement of crisis with the use of corticosteroids compared to traditional drugs [19]. Particularly controversial is the opinion if you establish a continuous antiepileptic therapy in patients who had isolated crises only at relapse [13].

In the management of patients with multiple sclerosis is important to note the comorbidity with epilepsy because often the presence of alterations discognitive transitional or temporary visual disturbances may represent the expression of symptoms of partial seizures and exacerbations of demyelinating disease. On the contrary the presence of such disorders in particular visual an epileptic patient may represent the onset of demyelinating disease. Accurate diagnosis in this sense allows no doubt setting targeted and effective therapeutic. Typically the antiepileptic treatment should take into account the general neurological condition of the patient with multiple sclerosis. In this regard the use of phenobarbital could accentuate cognitive deficits so it is recommended not to use it, or the use of carbamazepine, lamotrigine or gabapentin [21] could induce increased fatigue, disorders of balance, the cognitive slowing, the 'onset or aggravation of their symptoms of MS such disorders cerebellar, pyramidal signs, micturition disorders. Typically the new AEDs are all a viable therapeutic option for which the antiepileptic therapy in patients with multiple sclerosis does not involve particular difficulties of total employment.

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Citation (country)	n	Patients with seizures (percentage, 95% CI)	Predominant seizure subtype: Simple partial	Complex partial	Secondary generalized	Primary generalized
Hospital-based patient cohorts						
Berger, 1905 (Austria)[a]	206	3 (1.5%, 0.3–4.5%)	1			
Bau-Prussak & Prussak, 1929 (Poland)	268	13 (4.9%, 2.7–8.3%)	1	2	2	8
(Störring, 1940) Germany	205	13 (6.3%, 0.4–10.8%)	3	1	4	5
Müller, 1949 (Sweden)	810	28 (3.5%, 2.4–5.0%)	8		"major": 20	
Abb & Schaltenbrand, 1956 (Germany)[a]	1,420	25 (1.8%, 1.2–2.6%)				
Feldman, 1957 (Israel)	80	3 (3.8%, 1.0–11.3%)	1	0	1	1
Drake & Macrae, 1961 (USA)	289	13 (4.5%, 2.5–7.8%)	4	1	7	1
Matthews, 1962 (UK)[ab]	"approximately 200"	12		1	3	4
Hopf et al., 1970 (Germany)	3,606	19 (0.5%, 0.3–0.8%)	6	2	2	9
Cendrowski & Majkowski, 1972 (Poland)[c]	500	17 (3.4%, 2.1–5.5%)	3	1	7	6
Shibasaki et al., 1981 (Japan)[a]	60	5 (8.3%, 3.1–19.1%)				
(Shibasaki et al., 1981) UK[a]	204	2 (0.9%, 0.2–3.9%)				
Müller et al., 1986 (Germany)	450	8 (1.8%, 0.8–3.6%)	2	2	1	3
Büttner et al., 1989 (Germany)[a]	330	14 (4.2%, 2.4–7.2%)	3			9
Ghezzi et al., 1990 (Italy)[a]	1,459	34 (2.3%, 1.6–3.3%)				
Moreau et al., 1998 (France)	402	17 (4.2%, 2.6–6.8%)	13	0	0	4
Nyquist et al., 2001 (USA)[a]	5,715	85 (1.5%, 1.1–1.8%)	4	7	14	21
Sokic et al., 2001 (Serbia)	268	20 (7.4%, 4.7–11.4%)	2	1	14	3
Gambardella et al., 2003 (Italy)[a]	350	16 (4.6%, 2.7–7.5%)		5		2
Striano et al., 2003 (Italy)	270	13 (4.8%, 2.7–8.3%)	1	3	8	1
Pooled hospital-based studies[d]	16,892	348 (2.1%, 1.9–2.3%)	40 (22%)[h]	20 (11%)[h]	60 (33%)[h]	62 (34%)[h]
EEG examination studies						
Hoefer & Guttman, 1944 (USA)[e]	107	3 (2.8%, 0.7–8.5%)				
Fuglsang-Frederiksen & Thygesen, 1952 (Denmark)[e]	74	4 (5.4%, 1.7–14.0%)	3	0	1	0
Troullas & Courjon, 1972 (France)	132	10 (7.6%, 3.9–13.8%)	1	0	1	8
Pooled EEG examination studies	313	17 (5.4%, 3.2–8.7%)	4 (29%)[i]	0[i]	2 (14%)[i]	8 (57%)[i]
Population-based studies						
Oftedal, 1965 (Norway)[f]	127	3 (2.3%, 0.6–7.2%)	0	0	0	3
Ritter & Poser, 1974 (Germany)	812	5 (0.6%, 0.2–1.5%)	1	0	0	4
Kinnunen & Wikström, 1986 (Finland)[g]	599	21 (3.5%, 2.2–5.4%)	"partial": 7		5	9
(Engelsen & Gronning, 1997) Norway	423	17 (4.0%, 2.4–6.5%)	1	4	11	1
Olafsson et al., 1999 (Iceland)	188	5 (2.7%, 1.0–6.4%)	1	2	2	0
Eriksson et al., 2002 (Sweden)	255	20 (7.8%, 5.0–12.0%)	"partial": 6		2	12
Nicoletti et al., 2003 (Italy)	195	5 (2.6%, 0.9–6.2%)	0	0	4	1
Pooled population based studies	2,599	76 (2.9%, 2.3–3.7%)	3 (9%)[j]	6 (17%)[j]	17 (49%)[j]	9 (26%)[j]
All studies	19,804	441 (2.2%, 2.0–2.4%)	47 (20%)[k]	26 (11%)[k]	79 (34%)[k]	79 (34%)[k]

[a]Seizure type not specified for every patient; [b]One patient with tonic seizure excluded; [c]Including two patients with a single episode of primary generalized status epilepticus; [d]Excluding Matthews, 1962; [e]Four patients with syncope excluded; [f]Including one patient with a single primary generalized seizure; [g]Including two patients with a single primary generalized seizure; [h]Seizure subtype available in 182 patients; [i]Seizure subtype available in 14 patients; [j]Seizure subtype available in 35 patients; [k]Seizure subtype available in 231 patients.

Figure 1. Synthesis of published studies on seizures in patients with multiple sclerosis