Treatment of epilepsy in multiple sclerosis

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ABSTRACT

Purpose: The prevalence of epilepsy is increased in multiple sclerosis (MS), but information on AED treatment and seizure outcome is scarce. We describe epilepsy characteristics including the use of AEDs and proportion of seizure-free patients at two tertiary hospitals in Sweden.
Method: We retrospectively studied electronic medical records of all patients with a diagnosis of MS and seizures at Sahlgrenska university hospital and Uppsala university hospital. Clinical data were reviewed until 2017.
Results: We identified a total of 62 MS patients with at least one seizure. Median age at the first seizure (before or after MS) was 41 years (range 0–80). The most common MS disease course at the first seizure was secondary progressive MS, the neurological disability was considerable, and most patients had several MRI lesions at their first seizure. The first EEG demonstrated epileptiform discharges in 38% and unspecific pathology in 40%. Current seizure status could be determined for 37 patients. Out of these, 46% had been seizure free for more than one year at last follow-up. The majority of patients (65%) were on monotherapy at last follow-up. Carbamazepine was the most commonly used first AED, with a retention rate of 52%. No individual AED was associated with a particularly high rate of seizure freedom. The most common reason for discontinuation of the first AED was side-effects.
Conclusion: Seizure freedom rates were low, perhaps indicating a need for higher ambitions in management. Side effects of AEDs may be a particular concern when treating epilepsy in patients with MS.

1. Introduction

The new ILAE classification of epilepsies emphasizes aetiology and comorbidities [1]. Epilepsy in several distinct patient groups previously studied together under the term "partial epilepsy" are now studied in an aetiology-stratified manner; examples include poststroke epilepsy [2], autoimmune epilepsy [3], or epilepsy after infectious encephalitis [4,5]. In the era of person-centered care, such evidence is of great value for clinicians and health care providers trying to tailor therapy and management.

The prevalence of epilepsy is increased approximately threefold in multiple sclerosis (MS) [6,7]. Seizures are more common in severe MS, which suggests a causal relationship between accumulated brain damage and epilepsy [8]. In contrast to the acquired epilepsies listed above, investigators have so far focused on describing the co-existence of MS and seizures, and as pointed out in thorough reviews, little information is available on optimal AED treatment and epilepsy outcome [9]. This most likely reflects the relative rarity of epilepsy in MS and the subsequent low number of subjects available for study at individual centers. One study identified ten cases of epilepsy among 310 MS patients, seven of whom had good seizure control (defined as "few seizures") [10]. Another study reported that seizure control was easily achieved in 22/36 patients (61.1%), but did not provide information on AED treatment [11]. An attempt at a Cochrane review showed no eligible studies [9,12]. Recently, characteristics of epilepsy in MS was reported for 19 patients in a Norwegian single-center study, but the focus was not on epilepsy treatment and current seizure status [13]. In summary, there is shortage of systematic knowledge on management of epilepsy in MS. Given the increasing focus on aetiology in epilepsy, this is a considerable shortcoming – especially since worrying reports indicate that epilepsy in MS may have particular clinical characteristics; an unexpectedly high proportion of patients with status epilepticus and increased sensitivity to AED side effects [8,12].

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We therefore performed a retrospective observational study on patients with seizures and MS at two of Sweden's larger tertiary neurology centers, with focus on seizure prognosis and AED response.

2. Methods

2.1. Cohort

The electronic patient registers at Sahlgrenska University Hospital, Gothenburg and Uppsala University Hospital, Sweden, contain information on all outpatient and inpatient contacts at each hospital. We searched the databases for all contacts with the neurology department during available years (Gothenburg 2000–2013, Uppsala 2007–2016) and selected all patients with MS and at lest one code for seizure (R56.8) or epilepsy (G40.0-40.9). The search yielded 52 patients in Gothenburg and 15 patients in Uppsala. Among these, 47 patients in Gothenburg and 15 patients in Uppsala fulfilled the inclusion criteria (the records supporting at least one seizure and a diagnosis of MS). In five patients, the medical records revealed that the codes were erroneous, since either MS (n = 1) or seizures (n = 4) had not been present. These were excluded.

2.2. Review of records

Data were extracted from the medical records by use of a predefined clinical report form. EEG and MRI findings were categorized based on reports. Medical records were reviewed until April 2017 in Gothenburg and November 2017 in Uppsala and anonymized prior to analysis.

2.3. Statistics

Data are expressed as median and range for continuous variables and frequencies for categorical variables. Dates were approximated to the first day of the month or the year if the records did not contain exact information. If information was missing, the patient was omitted from that particular analysis. The exact number of patients in each analysis is given in tables or text. All analyses were performed using IBM SPSS version 23.

2.4. Ethical permission

The regional ethics committees of Gothenburg and Uppsala approved the study and waived the need for informed consent (Decisions Gothenburg 988-17 and Uppsala 397-17).

3. Results

3.1. Cohort and the first seizure

We identified 62 MS patients with seizures. Twenty-three patients were deceased. The median age at the first seizure was 41 years (Table 1). The first seizure type was focal with impaired awareness or focal to bilateral tonic-clonic in most cases, but tonic-clonic without clear focal onset in one third of cases (Table 2). The year of the first seizure and the year of onset of MS symptoms could be determined for 60 patients. In 82% of cases, the first seizure was considered unprovoked and in 87% of cases the seizure occurred after the MS-diagnosis (Table 2). For one patient in Gothenburg, a seizure was the presenting symptom of MS. The median time from diagnosis of MS to the first seizure was ten years, and from the onset of MS symptoms eleven years (Fig. 1). The most common disease stage at the time of the first seizure was secondary progressive MS, and the median expanded disability status scale (EDSS) score was 6.5 (0 = no disability, 10 = death in MS).

3.2. MRI and EEG findings

Twenty-nine patients had MRI results documented prior to their first seizure, with 93% demonstrating several lesions (semi-quantitatively assessed from reports or images, refers to all lesions – not just juxtacortical). An MRI after the first seizure was available for 42 patients, 88% of which had more than five lesions (unfortunately, most MRI reports did not specify lesion distribution). EEG was available for 52 patients; 40% demonstrated unspecific pathology such as slowing, and 38% had epileptiform discharges. Forty-four patients with EEG results available had more seizures, including all twelve patients with normal EEGs. Among the six patients that did not have more than one seizure, three had epileptiform discharges and three had unspecific pathology.

3.3. AED choice

Out of all 62 patients, 54 had additional documented seizures. Sixteen patients had other possible reasons for an epilepsy diagnosis such as CNS tumor (n = 4), head trauma (n = 7), stroke (n = 2), or other (n = 3). We next characterized the treatment and treatment response to AEDs in patients with seizures and no other aetiology than MS (Table 3). Information on the first AED could be found for 44 patients. The most commonly selected first drug was carbamazepine, followed by phenytoin, lamotrigine, and levetiracetam. Carbamazepine had been discontinued in almost half of the patients starting with this drug. For remaining AEDs, the numbers were small. The overall retention rate for the older AEDs carbamazepine, phenytoin, or valproic acid was 50% and that of newer AEDs lamotrigin, levetiracetam, gabapentin was 75% (p = 0.184, Fishers exact test).

3.4. Seizure outcome

At the time of last follow-up, seizure status could be determined for 37 patients (28 in Gothenburg and 9 in Uppsala). Among these, 50% had been seizure free for more than one year in Gothenburg and 33% in Uppsala. In total, 46% of patients were seizure free at last

Table 1
Cohort and follow-up time.

Demographics	Gothenburg		Uppsala		Total	
	n = 47	%	n = 15	%	n = 62	%
Male	12	25	6	40	18	29
Female	35	75	9	60	44	71
Deceased	21	46	2	13	23	38
Age and follow-up	Years, median	min-max	Years, median	min-max	Years, median	min-max
Age at 1st seizure	42	9–80	36	0–72	41	0–80
Age at last-follow-up	51	24–82	53	22–72	51	22–82
Time from 1st seizure	8	0–39	11	0–53	8	0–53