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Rethinking the importance of paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis: They do matter

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ABSTRACT

Background: Paroxysmal (PS) and unusual symptoms (US) as initial manifestation of multiple sclerosis (MS) are rare and often thought to indicate "benign" MS.
Objective: To investigate prevalence and clinical disease course of patients experiencing PS or US as first clinical manifestation.
Methods: Clinical, MRI and cerebrospinal fluid data of patients presenting with PS and US were obtained retrospectively and compared to patients with classical bout onset (CS).
Results: In a cohort of 1396 relapsing onset patients, 15 (1.1%) were identified as presenting with PS and 7 (0.5%) with US. Groups were comparable regarding gender, age at onset and intrathecal immunoglobulin synthesis ($p > 0.05$). During a mean follow-up period of 13.6 years, all patients presenting with PS or US converted to CDMS (mean duration 3.4 years; 95% CI 1.9–4.8) as compared to 1374 patients (94%) presenting with CS (mean duration 3.2 years; 95% CI 3.0–3.4; $p = 0.759$).
Conclusion: In a cohort of 1396 MS patients, 1.6% presented with PS or US at disease onset. Irrespective of the initial transient symptoms, patients were at the same risk of developing CDMS as CS patients, thereby underlining the importance of identifying PS and US as possible first clinical symptoms of MS.

1. Introduction

Although paroxysmal symptoms (PS) of multiple sclerosis (MS) are the expression of well-defined pathophysiological effects of demyelination on axonal conduction, they are among the most frequently misinterpreted manifestations of MS (Compston et al., 2005). Depending on the anatomical structures of the central nervous system involved, several clinical types of PS have been described. Typically, they are brief, lasting seconds to minutes, occur many times a day and are often stereotyped in a single patient (Compston et al., 2005). Symptoms appear suddenly and tend to continue in clusters with great intensity for days up to a few months.

Clinical relapses or attacks in MS have long been defined "as episodes of neurological disturbances for which causative lesions are likely to be inflammatory and demyelinating in nature that last for at least 24 h" (Polman et al., 2005). As a consequence, PS have not been considered to meet this definition. However, since the latest revision of the criteria in 2010 this definition of clinical relapses was generally maintained, but PS (historical or current) are now accepted as relapses as long as they consist of multiple episodes occurring over not less than 24 h (Polman et al., 2011). However, the clinical characteristics of PS are still not well defined, which can lead to inconsistent interpretations among neurologists (Gafson et al., 2012).

The prevalence of PS during any time of the disease course has been reported to be 8.6% (Eriksson et al., 2002), with a trend for manifestation early in the disease course (Tüzün et al., 2001). Although only anecdotally, PS have also been reported as first clinical manifestation of MS (Matthews et al., 1975; Twomey and Espir, 1980; Tüzün et al., 2001). Due to their self-limiting nature and often good response to anticonvulsive drugs, PS are often thought to indicate "benign" MS. However, there is no data on further clinical disease course after PS in MS so far.

Unusual symptoms (US) are thought to represent the clinical correlate of mainly cortical MS lesions. Focal epileptic seizures and various types of aphasia are among the more frequently reported

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phenotypes (Compston et al., 2005). The prevalence of US as initial manifestation of MS has not been reported so far.

Six randomized controlled trials (RCTs) have convincingly demonstrated the effectiveness of interferon ß, or glatiramer acetate and teriflunomide when initiated after a clinically isolated syndrome (CIS) on delaying the diagnosis of clinical definite (CD) MS (Jacobs et al., 2000; Comi et al., 2001; Kappos et al., 2006; Comi et al., 2009, 2012; Miller et al., 2014). These trials have included patients presenting with new or worsening neurological symptoms that were consistent with demyelination involving optic nerve, spinal cord, brain stem or cerebellum and were continuously present for at least 24 h. However, patients presenting with PS or US have either not been included (Jacobs et al., 2000; Kappos et al., 2006) or not reported (Comi et al., 2001, 2009, 2012; Miller et al., 2014).

In the presence of disease modifying treatments (DMT) that are highly effective in delaying or even avoiding further relapses when initiated early, data on further disease course of patients presenting with a PS or US at MS disease onset is needed.

2. Material and methods

2.1. Protocol, confidentiality, participants

In 2004 an electronic database was established at the MS Clinic of the Department of Neurology, Medical University of Innsbruck, which is the reference centre for MS in Western Austria. Data was collected retrospectively from patient's charts until 1987. From 2004 onwards, data was collected prospectively whenever the patient returned for scheduled (usually every 3–6 months, at least once yearly) follow-up or unscheduled visits. By November 2015, a cohort of 1651 MS patients has been included according to McDonald diagnostic criteria (Polman et al., 2005, 2011). The prevalence of MS in Austria is 148 per 100.000 people (Baumhackl, 2014). Given a population of about 1.6 million people in Western Austria, this study is likely to include most MS patients from this geographic area (Asamer et al., 2014). Confidentiality and data protection were ensured in keeping with the recommendations of the Austrian Data Safety Authority instructions (www.ris.bka.gv.at., 2016). Patients were included in case of diagnosis of MS with a relapsing remitting (RR) or secondary progressive (SP) disease course and a minimum follow-up period of five years. Since the definition of paroxysmal symptoms excludes a continuous neurological progression, patients exhibiting a primary progressive (PP) disease course were not included.

Collected demographic data included sex, age and clinical symptoms at disease onset, MS disease course (Lublin et al., 2014), time to first relapse, medical history and cerebrospinal fluid analysis. For the purposes of this study, relapses were defined as occurrences of new or worsening neurological symptoms, which lasted for at least 24 consecutive hours and were separated from each other by a minimum time interval of 30 days. Furthermore, relapses had to have been confirmed at our MS clinic. Clinical disability was incorporated using the Expanded Disability Status Scale (Kurtzke, 1983) (EDSS) and considered only when remaining stable for at least 6 months to avoid documentation bias due to EDSS changes related to relapses. Onset of secondary progression was defined retrospectively when sustained worsening of neurological symptoms (accounting for an EDSS progression of at least 1 point) was confirmed after a period of at least 12 months (Lublin et al., 2014).

2.2. Defining phenotypes of initial clinical presentation

According to the initial clinical presentation, patients were categorized into three subgroups: (1) classical bout symptoms onset, including attacks lasting continuously for at least 24 h (2) PS, as long as they are multiple and recur over at least 24 h and (3) transient unusual symptoms (US), including the clinical expressions of cortical lesions like repetitive short-lasting aphasia or focal epileptic seizures.1 In addition, data of patients presenting with PS or US were further evaluated for type of paroxysmal or unusual symptom, frequency and duration of one episode and MRI when performed within less than 100 days after symptom onset. MRI was rated according to Barkhof-Tintoré criteria (Barkhof et al., 1997; Tintoré et al.; 2000) by an experienced neuroradiologist (MW), who was blinded for clinical data. Furthermore, data of quantitative (IgG-Index) and qualitative (oligoclonal banding) intrathecal immunoglobulin production was included.

2.3. Statistical analysis

Variables are presented as median value and interquartile range or mean with 95% confidence intervals (CI) as appropriate. Differences between patient groups were evaluated using chi-square test, independent *t*-test and one-way ANOVA. Log-rank test was used to compare time to first relapse in the investigated subgroups. Significance was based on a p-value of < 0.05. Data was analysed using SPSS 19.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient sample, clinical presentations and prevalence

A total of 1396 confirmed MS cases with RR or SP disease course have been included in this study (Fig. 1). 15 patients (1.1%) presented with PS. PS presentations included trigeminal neuralgia (n=1), dysarthria and/or ataxia (n=3), tonic spasms (n=1), paroxysmal paraesthesia (n=4), diplopia (n=2) and akinesia (n=1). Furthermore, less commonly described PS, including paroxysmal paresis of upper extremities, facial myokymia and hemianopsia, were found (n=1 each). Twelve (80%) cases of PS led to immediate neurological consultation, three (20%) patients reported symptoms at time of first relapse. Frequencies of PS were equally balanced between occurring more and less frequently than ten times a day.

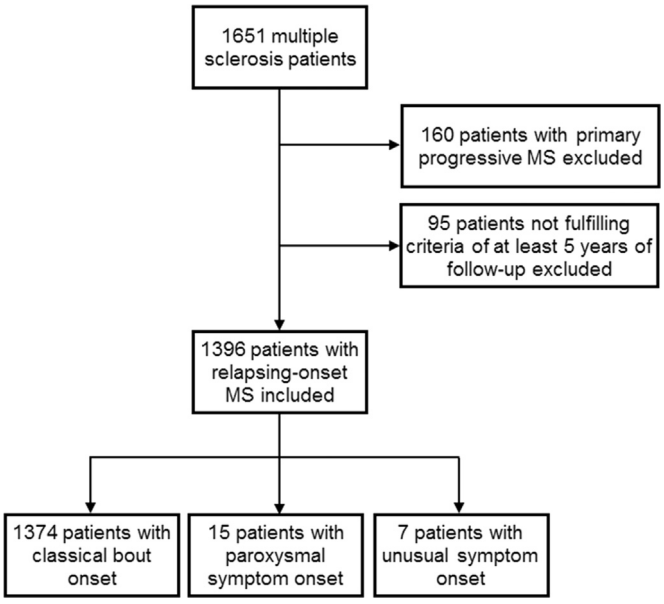

Fig. 1. Study flow chart.