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Natural history of benign multiple sclerosis: Clinical and HLA correlates in a Western Australian cohort

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ABSTRACT

Background: Benign multiple sclerosis (BMS) is a controversial term that has been used for MS patients with minimal disability decades after disease onset. Herein, we evaluated disease status after 20 years in a Western Australian cohort defined as BMS based on an Expanded Disability Status Scale (EDSS) score ≤ 3.0 at 10 years from onset.

Methods: MS patients with an EDSS score ≤ 3.0 at 10 years from onset and minimum of 20 years follow up were included in the study. The 20-year EDSS score was considered the primary outcome. Associations with demographic and clinical characteristics and HLA-DRB1 genotype were investigated.

Results: Among 120 patients with a benign course at 10 years, 78 (65%) remained benign at the 20-year follow up, but patients with an EDSS ≥ 2.5 were more likely to go on to develop more severe disability in the next decade. When considering factors associated with an increase in EDSS score ≤ 1 from 10 to 20 years, indicating limited progression, apart from the EDSS score at 10 years, poly-symptomatic presentation ($p = 0.004$) and cerebellar/brainstem mono-symptomatic presentation ($p = 0.016$) were independently associated with more rapid progression compared with other mono-symptomatic presentations. Carriage of the high risk HLA-DRB1*1501 allele was marginally associated with slower progression.

Conclusions: In this geographically isolated MS cohort of predominantly Anglo-Celtic origin clinical progression in the benign MS group was similar to that in other published series from Western countries. These results are in keeping with the view that patients labeled as benign MS are part of a heterogeneous continuum of disease progression and do not possess unique clinical characteristics. Possible genetic determinants of a benign course warrant further investigation.

1. Introduction

Multiple sclerosis (MS) is a chronic, heterogeneous, immune-mediated demyelinating disease of the central nervous system (CNS) with a peak incidence from the second to fourth decades [1]. It is characterized by myelin loss, axonal damage, and progressive neurological dysfunction and is notable for a variable course and prognosis [1]. Once MS is diagnosed, it is still difficult to predict if the disease will progress or will stay as a mild form with minimal disability and little progression many years after initial symptoms.

The majority of MS cases are characterized by clinical onset with relapses and remissions [relapsing remitting MS (RRMS)], after which the disease course typically develops inexorable secondary progression [secondary progressive MS (SPMS)]. There is a smaller group of MS patients who present with gradual progression and accumulation of disability without relapses [primary progressive MS (PPMS)]. In a minority of MS patients, however, the disease never leads to substantial disability and shows little or no progression years after the first

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symptoms, termed benign MS (BMS). It remains unclear whether such patients represent a distinct clinical subgroup of MS or are merely part of a continuum of disease and currently no reliable clinical, genetic, or laboratory prognostic markers exist to predict a benign course of MS.

The benign form of MS in most cases is determined using the expanded disability status scale (EDSS) score and the length of disease duration [2,3]. The most commonly used definition for selecting BMS cases is an EDSS ≤ 3.0 and at least 10 years after disease onset [4–7]. However, a wider range of EDSS scores (1.5–4.0) and longer disease durations (up to 50 years) have been used in some surveys [8,9]. The frequency of BMS in different studies has varied from 6% to 64% of all MS cases, depending on the evaluation criteria. Many older studies applied Poser's diagnostic criteria and did not include MRI findings, reducing the number of mild MS cases [10]. The lack of a standardized definition of BMS and differences in study design make it difficult to compare results from different cohorts. Moreover, relatively few studies have investigated the longer-term prognosis and predictors of outcome in patients classified as BMS at 10 years [6,8,11].

In the present study we evaluated disease status 20 years after onset in a cohort of patients initially categorized as having BMS at 10 years after diagnosis. The aims of the study were to determine how often there is a change in disease trajectory after the first decade, and to search for clinical or genetic markers that may be predictors of disease severity and clinical course.

2. Methods

2.1. Research participants

The study was a retrospective and prospective evaluation of patients with MS in Western Australia. All EDSS scores were calculated using the current Neurostatus scoring system. Patients registered in the Perth Demyelinating Disease Database (PDDD) diagnosed as having clinically definite or probable MS according to the Poser criteria [12] or McDonald criteria [13] were evaluated. One hundred twenty patients with a minimum of 20 years follow-up from the initial symptoms and an EDSS score ≤ 3.0 at 10 years from onset were categorized as benign MS and were enrolled into the study (Fig. 1).

We chose an EDSS score of ≤3.0 as the cut-off for BMS, as has been used in other recent studies, because such patients are still fully ambulatory and largely independent, albeit with mild-moderate disability.

Approval for the study was obtained from the Sir Charles Gairdner Hospital Human Research Ethics Committee (HREC No: 2006-073). Written informed consent was obtained from all participants in the PDDD cohort.

2.2. Clinical and laboratory data

Follow-up clinical information at 10 and 20 years, including EDSS scores, was obtained from the database or prospective clinical assessments. The majority of these patients were seen at least once a year. Data recorded included: gender, age at onset of initial symptoms (defined as the first episode of neurological dysfunction suggestive of demyelinating disease), disease duration, initial clinical course, number of relapses in the first two years, EDSS scores at 10 and 20 years from the onset, and use of disease modifying therapy (DMT). HLA-DRB1 genotyping data were available from 90 patients and results of CSF oligoclonal bands (OCB) in 39 patients [14].

We categorized country of birth into a Northern Hemisphere group (Europe), a Southern Hemisphere group (Australia and New Zealand) and others (Africa, Asia and the Middle East and North America) based on group size and plausible differences.

2.3. Statistical analysis

Categorical and continuous variables (BMS vs non-BMS) are presented as numbers of patients (%) or means ± standard deviations (SD), respectively. Ages at disease onset were compared using the *t*-test. Other prognostic factors (gender, relapses in the first two years and onset presentation) were compared using contingency table analyses (chi-squared or Fisher exact test as appropriate). Joint associations of EDSS scores with other variables were assessed using linear models for

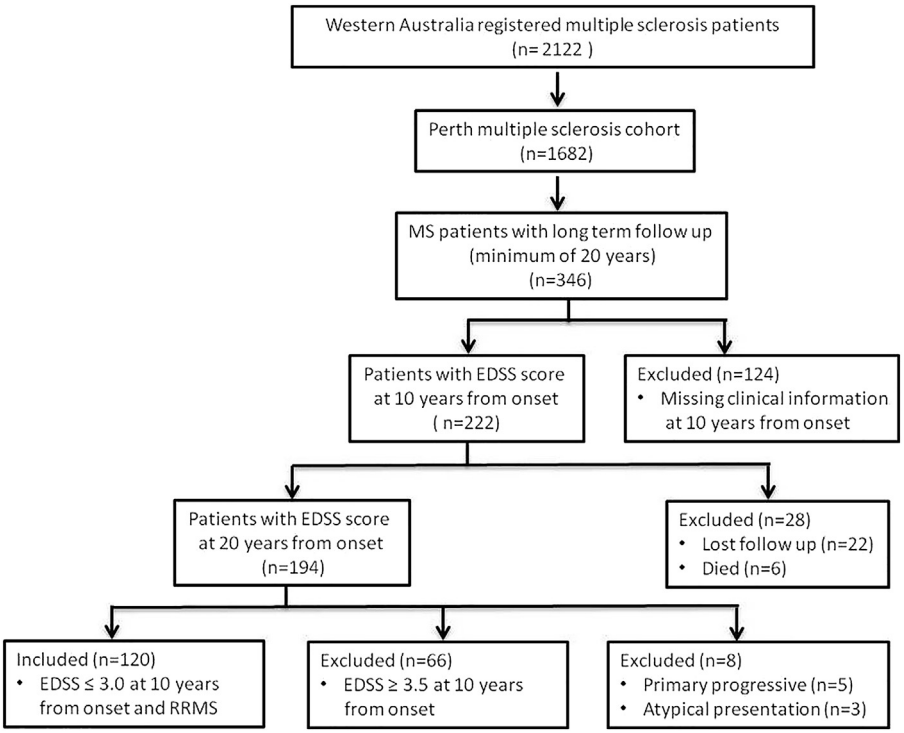

Fig. 1. The flow chart shows the successive selection process for the benign multiple sclerosis patients included in the study.
EDSS – Expanded Disability Status Scale.