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Review article

Predictive markers of disease evolution after a CIS in everyday practice

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ABSTRACT

Clinically isolated syndromes (CIS) indicate the possibility of developing multiple sclerosis (MS) over time in approximately 20–85% of the cases. Thus, accurately identifying which patients will present a second demyelinating episode and determining the degree of disability they could develop over the mid- to long term is considered crucial for a more individualized treatment. For this reason, a number of prognostic markers have been studied in an attempt to identify those that could provide additional information about the disease course. This review focuses only on markers with proven predictive power in CIS patients in the everyday clinical practice. In general, markers of conversion to clinically definite MS (CDMS) are more robust than those available for disability progression. More specifically, magnetic resonance imaging is, to this day, the most powerful tool for predicting both conversion to CDMS and disability progression in the mid-term. Other useful markers include the age of onset and the presence of oligoclonal bands in cerebrospinal fluid. Identifying a practical marker that improves the prognostic value of the available tools remains an unmet need.

Contents

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1. Introduction

A clinically isolated syndrome (CIS) is a term used to define an acute or subacute episode suggestive of central nervous system (CNS) inflammatory demyelination [1]. A CIS, in turn, suggests the possibility of developing multiple sclerosis (MS) over time in a percentage of patients ranging from 20% to 80%, depending on the presence of certain baseline features [2]. Current evidence suggests that disease modifying treatment (DMT) should be started at this stage since it is likely to have an important impact on the evolution of the disease [3]. Furthermore, several clinical trials in CIS have demonstrated that DMT delays conversion not only to CDMS [4–7], but also to McDonald MS [6]. On the other hand, arguments against early treatment include exposing patients who will not evolve to MS to medication adverse events, particularly the more recently approved drugs [8], or modest clinical benefits in the long run [9]. Thus, accurately identifying which patients will present a second demyelinating episode and, above all, determining the degree of disability they could develop over the mid- to long term are considered crucial for a more individualized treatment. For this reason, a number of predictive markers have been studied in an attempt to identify those that could provide additional information about the disease course. Although there are many markers under research, this review will focus only on those with proven predictive power in patients with CIS in everyday clinical practice. The sections of this discussion will include the demographic and clinical factors, magnetic resonance imaging (MRI), oligoclonal bands (OCB), and evoked potentials (EP). Conversion to MS and disability progression will be discussed separately in each section. Regarding the latter, it is important to note that there is no consensus about an ideal definition to date: different studies have used different definitions, making this endpoint less well defined than presenting a second attack or radiological dissemination in space and time. Whenever possible, the used definition of disability progression will be specified throughout the text. The most common are: disability milestones according to observational studies, three-month sustained increase of 0.5 or 1.0 point in the expanded disability status scale (EDSS) or time to reach moderate disability (EDSS 3.0). Finally, a smaller section on future challenges will describe markers that could eventually be used in the clinical practice.

2. Demographic and clinical factors

2.1. Conversion to clinically definite multiple sclerosis

2.1.1. Age and gender

Subgroup analysis in the BENEFIT clinical trial showed that, in two years, the risk of conversion to clinically definite MS (CDMS) in the placebo group was higher in patients younger than 30 years of age; the trial included CIS patients with two or more subclinical lesions on baseline MRI [10]. Another study showed that a younger age at the time of CIS was an independent predictor of conversion to CDMS in CIS or relapsing–remitting MS (RRMS) patients seen within the first year of disease onset after adjusting for treatment. Non-white ethnicity was also an independent predictor of conversion in this study [11]. In a long follow-up study of patients with unilateral optic neuritis, younger patients also had a higher risk of developing MS [12]. As for gender, no clear consensus about its influence on conversion to CDMS exists: whereas a recent meta-analysis showed a marginal increase, with a risk of 1.20 (95% CI 0.98–1.46) for females in comparison to males to develop MS after a CIS [13], in other single centre study gender does not appear to have a strong influence on the development of a second demyelinating episode [11].

2.1.2. CIS topography

A few studies have shown that less CIS patients presenting with optic neuritis convert to CDMS or that it takes a longer period for these cases to suffer a second demyelinating episode in comparison to CIS affecting other topographies [2,12]. However, these results were obtained without taking possible confounding factors in consideration. For instance, when adjusting for CSF findings, the presence of pleocytosis or of OCB in cerebrospinal fluid (CSF) of patients with optic neuritis increased the risk of conversion to CDMS in comparison to those with normal CSF in one long-term follow-up study [12]. Similar results have been obtained when studying optic neuritis and the role of brain MRI as a covariate has been addressed: another study demonstrated that CIS patients with optic neuritis have a lower percentage of conversion to CDMS and are less likely to have OCB in the CSF than CIS cases affecting other topographies; however, it was observed that 50% of patients with optic neuritis have a normal brain MRI in comparison with 25% or less in other CIS topographies. Taking this into account, when only optic neuritis cases with an abnormal MRI were studied, the risk of conversion to CDMS was very similar for all CIS topographies [14]. Thus, visual onset seems to have a better prognosis for conversion due to the higher number of normal brain MRIs. Regarding CIS affecting other topographies, a small retrospective study showed that in CIS of the brainstem or cerebellum, the presence of facial sensory symptoms predicts a lower risk of conversion to CDMS in comparison to gait disturbances or diplopia [15].

2.1.3. Monofocal vs multifocal CIS

A CIS is, by definition, monofocal; however, multifocal presentations have also been considered [16]. Whether this is a prognostic factor for conversion remains somewhat controversial. In the ETOMS clinical trial, multifocal onset was one of the baseline variables that significantly predicted conversion to CDMS, with a risk twice as high in comparison to monofocal presentations (odds ratio = 1.99, 95% CI 1.14–3.46, $p = 0.015$) [5]. On the contrary, an observational study demonstrated that, in a multivariate analysis, a lower number of affected functional systems predicted an increased risk of converting to CDMS within one year [11], and the BENEFIT clinical trial subanalyses showed that patients with monofocal presentations had a higher risk of conversion to CDMS in the placebo arm of the study [10], whereas in one CHAMPS clinical trial subanalysis that reclassified 30% of patients as having multifocal disease at baseline based on functional system scores, it was shown that DMT delayed conversion to CDMS in cases with monofocal presentations ($p = 0.0013$) [17]. Furthermore, it was the monofocal presentations with nine or more lesions or at least one gadolinium-enhanced lesion on MRI that presented the higher risk of conversion [10]. This observation was later supported by another study in which time to CDMS was similar between monofocal and multifocal CIS patients; however, when taking into account the number of T2 lesions or the presence of gadolinium-enhanced lesions, the risk of developing a second demyelinating event was significantly higher in patients with monofocal presentations [18]. In all, it may seem that the risk of converting to CDMS is probably higher in cases with more typical, monofocal presentations with a brain MRI suggestive of MS, although further studies might be needed in order to obtain more conclusive results.