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Multiple Sclerosis on behalf SFSEP

Multiple sclerosis biomarkers: Helping the diagnosis?

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ABSTRACT

Multiple sclerosis (MS) is a complex heterogeneous disease. Diagnostic criteria are based on symptoms, biomarkers, MRI data and exclusion of differential diagnoses. Over the past few years, the usefulness of biomarkers has progressively decreased with the development of new MRI criteria, yet dozens of new biomarkers, especially in cerebrospinal fluid, for MS diagnosis and prognosis have been described. Large-scale studies validating some of these new biomarkers have also provided confirmation of a restricted set of biomarkers (presented here in this review) as having potential value for different stages of the disease, including as early as clinically isolated syndrome and radiologically isolated syndrome. However, differentiating progressive forms of MS from relapsing–remitting MS remains a genuine challenge, and could help to predict future conversion to secondary-progressive MS. In addition, new approaches combining multiple biomarkers might allow us to unravel the complexity of the disease and determine disease stages more precisely. Moreover, recent technological developments allowing analysis of biomarkers in plasma have also provided less invasive analysis of MS, and should serve to predict MS evolution and therapeutic responses during follow-up.

1. Introduction

Multiple sclerosis (MS), the most frequent inflammatory disease of the central nervous system (CNS), generally affects young adults. Active MS, including clinically isolated syndrome (CIS) and relapses arising either alone or during the progressive phase of MS, is associated with focal inflammation and neuroaxonal injury, while progressive MS involves diffuse CNS inflammation and neurodegeneration. In both cases, dissemination in space (DIS) and dissemination in time (DIT) of CNS lesions are the two main characteristics of this chronic disorder. MS diagnosis remains one of exclusion of other neuroinflammatory diseases, although clinical, magnetic resonance imaging (MRI) and biological characteristics often provide clear suggestive features of the disease, thereby fulfilling diagnostic criteria. Oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) represent the only useful biomarker

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for diagnosis of primary-progressive MS (PPMS), although they are also present in > 90% of relapsing–remitting MS (RRMS) cases, and can be helpful when diagnostic criteria are not met on MRI.

Over the past decade, several other CSF and serum biomarkers associated with inflammation of the neurodegenerative process have been discovered in MS patients through proteomics and genomics, and validated in yet other studies. Moreover, recent technological developments allowing analysis of biomarkers in plasma (such as neurofilament light chain and microRNA assays) have provided less-invasive tools. However, compared with MRI and CSF, their limited contributions (mainly due to lack of specificity) to MS diagnosis do not permit their inclusion in diagnostic criteria at this time. Nevertheless, they remain highly informative in atypical cases of MS. The present review discusses the usefulness of biomarkers in the diagnosis of different forms of MS.

2. Biomarkers of differential diagnoses

An MS diagnosis is often considered in cases of acute onset of CNS symptoms, but the assertion requires exclusion of other diseases potentially mimicking MS. Some of these mimics have their own specific biomarkers, making a thorough diagnostic workup essential, especially in cases of optic neuritis and transverse myelitis. Classic CSF analysis can provide data suggesting an inflammatory or infectious differential diagnosis in cases where a large number of CSF cells are present (meningitis) and protein levels are elevated. In 2005, specific antibodies against aquaporin-4 (anti-AQP4) were identified in 60–75% of patients with neuromyelitis optica (NMO) [1]. Since then, clinical presentations other than optic neuritis and longitudinal extensive transverse myelitis (LETM) have been associated with anti-AQP4 antibodies and constitute NMO spectrum disorders (NMOSDs) [2]. Anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies, previously associated with acute demyelinating encephalomyelitis (ADEM) in children [3], have also recently been found to be present in around half of seronegative NMOSD adult patients [4,5]. Their prognosis appears to be better than those of patients with anti-AQP4 antibodies. Moreover, high levels of interleukin (IL)-6 in CSF suggest a differential diagnosis other than MS, including NMO, ADEM and systemic lupus erythematosus [6].

After comprehensive analyses in which these differential diagnoses, and eventually others, have been ruled out, more clues need to be gathered to support an MS diagnosis.

3. Importance of biomarkers in RRMS diagnosis

After CIS, the challenge is to predict, with sufficient accuracy, conversion to clinically definite MS (CDMS), as many patients remain asymptomatic even with long-term follow-up [7]. Intrathecal synthesis of immunoglobulin G (IgG; also called 'positive CSF'), defined by the presence of OCBs and/or an elevated IgG index, constitutes an historical biomarker of MS [8]: it was included in the biological criteria for MS diagnosis in Poser's criteria, proposed in 1983 [9]. After CIS, intrathecal IgG synthesis was also considered useful for proving DIS in the McDonald criteria when Barkhof criteria were not fulfilled [10–12]. However, in 2006, Swanton et al. [13] proposed simpler criteria for DIS without compromising specificity and accuracy. These were used in the 2010 McDonald revision and abandoned CSF analysis to prove DIS for a diagnosis of RRMS [14]. In fact, a return to older DIS criteria seems to have taken place from the last modification of MS diagnostic criteria proposed by the MAGNIMS (Magnetic Resonance Imaging in Multiple Sclerosis) group in 2016 [15]. However, those 2016 criteria suggest that MRI has reached its limits in terms of predicting conversion from CIS to CDMS [16]. Indeed, OCBs and/or new biomarkers of conversion, including several CSF and serum biomarkers, should be integrated into analyses of large cohort studies to establish their accuracy for MS diagnosis in CIS patients.

3.1. *Immunoglobulins (Igs)*

CSF OCB and IgG indices have been assessed for predicting conversion to MS after CIS in many studies, and have variable sensitivity (from 80% to 91%) and specificity (from 86% to 94%) [17,18]. Although conversion rates are highly variable with odds ratios (ORs) ranging from 2.18 to 9.3 [19–21], these results are also promising, particularly for conversion after CIS with optic neuritis or transverse myelitis [22]. A large meta-analysis by Dobson et al. [23] involving 2685 CIS patients showed an elevated risk for CDMS when OCBs were present (OR: 9.88). In a prospective cohort of 1058 CIS patients, multivariate analysis showed that the presence of OCBs constituted an independent prognostic risk factor for conversion to CDMS [adjusted hazard ratio (HR): 1.3, 95% confidence interval (CI): 1.0–1.8], albeit less accurately than MRI data: HR: 5.1, 95% CI: 2.9–8.9, for one to three lesions; HR: 7.5, 95% CI: 4.3–13.1, for four to nine lesions; and HR: 11.3, 95% CI: 6.7–19.3, for ≥ 10 lesions [24]. Moreover, the Barcelona cohort also confirmed that the presence of OCBs and > 10 T2-weighted lesions on baseline brain MRI were the only predictors of accumulation of disabilities (HR: 2.0, 95% CI: 1.2–3.6, and HR: 2.9, 95% CI: 1.4–6.0, respectively). The study confirmed the important role of OCBs in predicting both conversion to MS and disability accumulation after controlling for other demographic, clinical, disease-modifying therapy (DMT) and MRI variables.

Few studies have explored the importance of identifying specific subtypes of IgGs and other types of intrathecal Igs (IgM and IgD) [25]. However, the renewed interest in intrathecal IgM since 2010 (when the revised McDonald criteria changed those for CDMS) has shown its possible predictive role in conversion [20,26–28]. Interestingly, in a series of 205 CIS patients, the presence of IgM OCBs correlated with early conversion [26].

The presence of kappa free light chains (KFLCs) and lambda free light chains (LFLCs) in CSF was identified at about the same time as IgG OCBs. In fact, KFLC intrathecal synthesis and index may have greater specificity and sensitivity than IgG OCBs and IgG index for diagnostic purposes [29–32], and have sometimes been found in CIS patients testing negative for OCBs [17,33]. Looking at conversion from CIS to CDMS, higher levels of CSF KFLCs have been found in CIS converters vs non-converters, with greater sensitivity and specificity than OCBs

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