Biological Markers of Prognostic Value in Multiple Sclerosis

a report by

Franziska Di Pauli, **Markus Reindl** *and* **Thomas Berger**

Neuroimmunological and Multiple Sclerosis Clinic and Research Unit, Clinical Department of Neurology, Innsbruck Medical University

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Multiple sclerosis (MS), a chronic inflammatory disorder of the central nervous system (CNS), is the most common neurological disease among young adults, and carries the potential risk of permanent disability. The pathological hallmarks of the disease are multifocal white (and, most recently, also grey) matter lesions, which are characterised by variable extents of inflammation, demyelination, axonal loss, gliosis and atrophy.[1] MS has variable clinical presentations and highly heterogeneous disease courses, ranging from rare acute fulminate forms to benign MS without substantial disability. Eighty-five per cent of patients initially present with a clinically isolated syndrome (CIS); most of these patients go on to develop relapsing–remitting (RR) MS, with acute relapses alternating with periods of clinical remission or stability.[2] Ultimately, more than half of (untreated) RRMS patients convert to secondary chronic progressive (SP) MS, which is characterised by accumulating neurological disability with or without superimposed relapses.[3] The clinical outcome of MS is largely unpredictable for individual patients. The great variability of this complex disease highlights the need for reliable biological markers with high sensitivity and specificity that are able to predict the future disease course and treatment response. Furthermore, stratification of MS patients with regard to their dominating pathological processes would allow individualised differential therapeutic concepts. In this review, we discuss the prognostic value of biological markers that are currently under debate, including magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) parameters and antibodies.

Franziska Di Pauli is a staff member of the Neuroimmunological and Multiple Sclerosis Clinic and Research Unit in the Clinical Department of Neurology, Innsbruck Medical University, where she is enrolled in the PhD programme in neurosciences. Her main research interests in multiple sclerosis are biological markers with their neuroimmunological, clinical and magnetic resonance imaging correlations and the impact of environmental factors.

Markus Reindl is an Associate Professor of Neuroscience and Head of the Neurological Research Laboratory in the Clinical Department of Neurology at Innsbruck Medical University. His main interest is clinical immunology of multiple sclerosis, with a strong research focus on antibodies and B cells.

Thomas Berger is an Associate Professor of Neurology and Head of the Neuroimmunological and Multiple Sclerosis Clinic and Research Unit in the Clinical Department of Neurology at Innsbruck Medical University. His main scientific interests regard immunopathogenetic heterogeneity of multiple sclerosis and the identification and characterisation of diagnostic/prognostic biological markers in multiple sclerosis.

E: thomas.berger@i-med.ac.at

Markers to Predict Disease Progression

Magnetic Resonance Imaging as a Prognostic Marker

MRI is a well established tool for the diagnosis[4] and management of MS that allows disease activity and progression to be monitored. The lesions detected on T2-weighted and gadolinium (Gd)-contrast-enhanced T1-weighted MRI reflect the pathological hallmark of the disease: the T2 lesion burden seems to be correlated with the number of preceding relapses[5] and the use of Gd enables visualisation of blood–brain barrier disruption and therefore inflammatory disease activity.[6] Thus, MRI has become a relevant surrogate outcome marker in MS clinical trials. Doubtless, MRI has its greatest relevance in patients with a CIS: evidence of dissemination of MS lesions in space and time and the extent of MRI activity are robust predictors of a first relapse.[7,8] However, since commonly used MRI techniques show only a weak association with future disability,[9] their prognostic value is limited and they are not useful for predicting clinical outcome in individual patients.[10] Poor clinico-radiological correlations may be due to either insensitive clinical rating scales or methodological difficulties in the detection of pathological alterations, especially axonal damage, within the normal-appearing white (NAWM) and grey matter (NAGM).[10,11] Neuropathology demonstrates that axonal loss, which seems to be the substrate of accumulating disability, occurs not only in classic MS plaques but also in NAWM and the cortex. Imaging of axonal loss and further brain atrophy is not sufficiently reflected by conventional MRI techniques. Although it has been suggested that the degree of disability depends mainly on the extent of brain atrophy,[13] until now it has not been commonly agreed upon as a prognostic marker. Newly emerging and innovative MRI techniques, such as higher-resolution imaging, brain volumetry, magnetisation transfer imaging and magnetic resonance spectroscopy, and the combination of these different imaging parameters, will be more predictive for disease progression in MS patients in the future.

Oligoclonal Bands

The qualitative and quantitative measurement of elevated immunoglobulins (IgG) in the CSF of MS patients is the only laboratory biomarker included in MS diagnostic criteria. Isoelectric focusing (IEF) is the best qualitative method for detection of oligoclonal bands (OCBs),[14] and has a sensitivity higher than 95% in MS[15] and a specificity generally considered to be more than 86%.[14] The value of the presence of OCBs to predict future disability remains controversial.[16,17]

IEF also allows the detection of oligoclonal IgM bands,[18] which seem to be predictive for a more severe disease course with a shorter time period

to the next relapse, an earlier disease conversion to SPMS and a higher grade of disability.[19] These results need further evaluation in prospective multicentre studies concerning both the methodical procedure and the prognostic specificity and sensitivity before IgM OCBs can be used as markers in clinical practice.

> In this review, we discuss the prognostic value of biological markers that are currently under debate, including magnetic resonance imaging, cerebrospinal fluid parameters and antibodies.

Antimyelin Antibodies

Antibodies directed against myelin-oligodendrocyte-glycoprotein (MOG), which is exclusively localised on the surface of myelin sheaths and oligodendrocytes,[20] and myelin basic protein (MBP), which constitutes 30% of total central myelin protein,[21] have been suggested to predict future disease progression in patients with a CIS.[22] The results of several subsequent studies were conflicting and ranged from highly significant[22–24] to significant in sub-analyses[25,26] to not significant at all.[27–29] The different studies were all performed with the same type of assay for antimyelin antibodies, i.e. immunoblotting, thus the inconsistent results are likely due to varieties among the study cohorts. Whether antimyelin antibodies will be useful for clinical practice remains to be established.

Neuromyelitis Optica

Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder that selectively affects the spinal cord and optic nerves.[30] NMO was generally regarded as a subtype of MS with a high risk of severe disability and mortality. Recently, the presence of NMO-specific autoantibodies, NMO IgG, was proved,[31] which supports the hypothesis that humoral immunity plays an important role in the pathogenesis of NMO.[32] Aquaporin-4, a water channel located in astrocyte foot processes at the blood–brain barrier, has been identified as target antigen.[33] NMO IgG is the first antibody of diagnostic value in a demyelinating CNS disease and

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distinguishes NMO patients from those with classic MS and other inflammatory MS variants. Furthermore, detection of NMO antibodies in patients with recurrent optic neuritis or with initial occurrence of longitudinally extensive transverse myelitis seems to predict subsequent relapses.[34,35] In future, this may render early identification of NMO patients possible, thus allowing a rapid start with specific therapies such as plasmapheresis[36] or B-cell-selective treatments.[37]

Markers to Predict Treatment Response

Interferon-β

Interferon-β (IFN-β) is one of the first-line disease-modifying therapies in MS and significantly reduces clinical and MRI disease activity. However, only half of patients respond well.[38,39] Therefore, the identification of biomarkers to predict treatment responses and failures would be of great value to individualise patient management.

Biological treatments are well known to induce to some extent antidrug antibodies, which are responsible for the decrease/blockade of treatment effects and the occurrence of adverse events. A significant percentage of IFN-β-treated MS patients develop neutralising antibodies (NAb) to IFN-β.[40] NAb-positive patients show higher relapse rates and more disease activity on MRI than NAb-negative patients, which confirms the clinical importance of NAb.[41] NAb titres are variable and may change over time. They usually appear in the first year of treatment,[42] and their occurrence depends on the immunogenicity and route of administration of the IFN-β product, as shown by lower frequencies for intramuscular administration, for example.[43] Several guidelines on the use of anti-IFN-β antibody measurements (e.g. by a European Federation of Neurological Societies Task Force)[44] recommend NAb testing after 12 and 24 months of IFN-β

> Antibodies directed against myelin-oligodendrocyte-glycoprotein have been suggested to predict future disease progression in patients with a clinically isolated syndrome.

treatment. In NAb-positive patients, a further NAb test after three to six months is needed to confirm NAB persistency. IFN-β therapy should consequently be discontinued in patients with persistent high NAb titres.[44] This strategy allows the risk of treatment failure to be minimised, because high NAb titres clearly precede their adverse clinical consequences and patients can thus be switched to alternative treatment options. More recently, other strategies, such as genetic or genomic approaches, have tried to identify factors that allow prediction of treatment responses,[45] e.g. determination of the immunogenicity of IFN-β with regard to the future risk of NAb development.[46]

Natalizumab

Natalizumab is a humanised monoclonal antibody that binds to very late activation antigen 4 (VLA-4), an α4β1 integrin, and thereby prevents the migration of leukocytes through the blood–brain barrier. NAb to natalizumab occur early (usually within three months) during treatment and are persistent in 6% of patients. These NAb increase drug clearance and competitively block active drug binding to VLA-4.[47] Thus, persistent NAb to natalizumab antagonise the otherwise very good treatment effects on relapse rate and disease activity.[47] Furthermore, persistent NAb are associated with more hypersensitivity adverse reactions, which also mainly occur within the first three months of treatment. Again, once testing for NAb to natalizumab is routinely used it will constitute a risk minimisation tool regarding hypersensitivity reactions and future treatment failures for individual patients.

Another severe adverse advent during treatment with natalizumab regards the risk of progressive multifocal leukoencephalopathy (PML), wh-ch has been estimated as one case per 1,000 natalizumab-treated patients over 18 months.[48] Despite extensive studies, no prognostic marker could be identified that allows determination of the risk of PML in advance.[49]

> The heterogeneity of multiple sclerosis requires reliable (differential) diagnostic and prognostic markers for individual counselling and therapeutic management.

Conclusion

The heterogeneity of MS in terms of clinical presentation, genetic background and pathological and immunological features requires reliable (differential) diagnostic and prognostic markers for individual counselling and therapeutic management. Numerous studies have tried to identify such a (panel of) biomarker(s) with high specificity and sensitivity to define patients according to their suggested immunological phenotype, to determine the prognosis of disease progression and to predict treatment responses. Some substantial progress can be noted, such as new MRI techniques, NMO-IgG antibodies or NAb to IFN-β or natalizumab. However, much more effort is necessary to reach the goal of prognostically valuable biological markers to anticipate future disease course and treatment response in individual patients. Emerging biotechnical methods and increasing insight into the underlying pathomechanisms will discover new biomarker candidates, which should, after careful validation, improve the perspective and management of MS patients. ■

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