Clinical, Biochemical and Imaging Parameters that may be Predictive of High Disease Activity, Rapid Progression or Increased Disability in Multiple Sclerosis

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Abstract

Increased ability to predict disease course and response to disease-modifying therapies in multiple sclerosis (MS) would optimise treatment outcomes by guiding selection of patients for a particular therapeutic intervention. Several factors affecting disease progression have been identified, including individual characteristics such as age at onset and race, onset of symptoms, early disease outcomes and radiological measures. While studies of magnetic resonance imaging (MRI) prognostic indicators have given mixed results, advances in technology are increasing the predictive power of MRI, and new techniques and outcome measures are providing alternative means of predicting disease course and response to treatment. The search for a predictive biomarker is an area of active research but studies remain poorly validated. Potential biomarkers include neurofilament proteins, microRNAs, gene expression and antibodies. Since it is unlikely that a single factor may predict disease course, a number of composite scoring systems have been proposed, but none have yet received widespread acceptance. However, it seems likely that in the future, a combination of MRI and biochemical biomarkers will provide a foundation for therapeutic decision-making in MS allowing an individualised approach.

Keywords

Multiple sclerosis, biomarkers, magnetic resonance imaging, clinical indicators, prognostic factor, gene expression profiling, composite score

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Advances in diagnosis, imaging and clinical monitoring have significantly improved our understanding of multiple sclerosis (MS), although the factors affecting prognosis of this heterogeneous condition remain poorly understood. Early intervention with disease-modifying treatments has been shown to optimise long-term clinical outcomes and a range of therapies are now available with varying risk–benefit ratios. Immunomodulatory agents for the relapsing–remitting form of the disease (RRMS) can reduce the relapse rate and slow the accumulation of disabilities but they are expensive and some have potentially serious side effects. Predictors of response to treatment would be valuable for selecting appropriate patients for particular treatments and preventing unnecessary therapy in non-responders.

A recently published 30-year observational study has indicated that favourable 10-year disability scores fail to ensure a long-term benign course of MS, and additionally, every decade almost half of the patients categorised with clinically definite benign MS (CDBMS) were no longer benign.[1] At the time of diagnosis, a need exists for better prognostic factors of the future disease course. These will enable clinicians to distinguish between patients who are likely to develop disability, where early aggressive intervention is warranted, from those who are likely to have a more benign course. Prediction of disease progression can also be useful in the design of clinical trials for selecting active patients.

With the number of therapies currently available, it is extremely difficult – if not impossible – to establish reliable post-treatment prognostic markers since a patient's prognosis is possibly altered by the drugs. As a result, the only true and reliable prognostic markers are those from the pre-treatment era, which consist of clinical variables based on natural history studies[2–4] and magnetic resonance imaging (MRI) studies.[5,6] Several studies have also suggested that global atrophy is a good surrogate marker of disease progression.[7,8] This article will review what is known about predicting prognosis in MS patients and the potential of different techniques and biomarkers to monitor disease course.

Clinical Indicators of Disease Progression

Several studies have attempted to correlate factors at presentation with adverse outcomes in MS and a summary of factors affecting disease progression including demographics, onset of symptoms, early disease outcomes and radiological measures is given in *Table 1*. Although studies have yielded mixed results, strong evidence has

been presented of associations between poor prognosis and older age at onset, male sex, sphincter symptoms at onset, incompleteness of recovery from the first attack and short interval between the first and second attack.[4,9–15] Contrary to these studies, it is now generally agreed that younger age at onset is associated with worse prognosis.[16] Nevertheless, these early factors have no predictive ability once permanent disability occurs (defined as 4 on the Expanded Disability Status Scale [EDSS]).[2]

An analysis of 821 patients suggested that relapse number prior to entry into clinical trials together with disease duration are predictors for on-study relapse rate.[15] Mesaros et al. noted that when assessing the value of clinical and MRI variables in predicting clinical outcomes in RRMS patients, baseline measurements only modestly predict short-term accumulation of brain atrophy and disability.[17] However, clinical progression was independently correlated with higher EDSS and T2 lesion load at baseline. While most studies agree that the factors above predict at least short-term progression, there is wide inter- and intra-patient variability in clinical severity as well as the rate of progression of MS.

Clinical variables such as age, gender, age at disease onset and initial symptoms, from large natural history studies, have been found to significantly influence the time from the onset of MS to moderate disability (a score of 4 on the Kurtzke Disability Scale), but not the subsequent progression of disability.[2] It has long been established that with frequent or severe relapses, or relapses that occur further into an MS disease course, it is more likely that deficits will persist.[18]

The symptoms associated with a relapse, such as motor versus sensory, and the localisation of lesions causing a relapse, may be important prognostic factors. Little association has been found between sensory symptoms and disease course in MS.[19–21] An attack of optic neuritis is more favourable than severe ataxia, which has been associated with multiple relapses.[22] Sphincter, or motor, or motor-sensory symptoms, have been found to be predictive of the onset of secondary progressive course in RRMS.[10]

Certain demographic factors are indicative of a poor prognosis. Early studies suggested that relapse rates were not affected by age at onset.[2] However, more recently, a study found a significant inverse relationship between age at MS onset and relapse rate in the univariate analysis but not in the multivariate analysis.[15] Another study found a non-significant trend between younger age at MS onset and the occurrence of relapses.[23] Furthermore, relapses are more frequent in patients with paediatric-onset compared with adult-onset MS.[24] A recent study found that age of disease onset had little effect on the progressive course of MS.[25] Findings regarding associations between gender and MS disease course have been mixed, although several studies have indicated that a poor prognosis is related to male gender.[26–28]

Race and ethnicity are important prognostic factors. African Americans have a lower risk of developing MS than Europeans, which may be related to genetic susceptibilities.[29] It has also recently been reported that the major histocompatibility complex appears to play a smaller role in MS susceptibility in African Americans.[30] However, compared with Caucasian Americans, African American patients, and to a greater extent Asians with MS, have a greater likelihood of developing opticospinal MS and transverse myelitis, and have a more aggressive disease course.[31] Similar findings were observed in a comparison of North African and European MS patients.[32] A recent study found greater tissue damage and faster lesion volume accumulation in African Americans relative to Caucasian Americans.[33] Differences in disease onset and course have also been observed in Hispanic patients.[34]

Past and current smoking is associated with measures of disease activity (clinical relapses and development of new lesions visible on MRI), more rapid conversion from a clinically isolated syndrome (CIS) to confirmed MS,[35] increased rate of conversion from RRMS to secondary progressive MS (SPMS),[36,37] and the rate of neurological deterioration once progressive MS has been established.[38] These associations are strongest in those with early smoking debuts, which also affect MS phenotype significantly.[39] Like smoking, vitamin D deficiency has been associated as a risk factor for MS, but whether vitamin D levels effect the prognosis of the disease is still being

Table 1: Factors Predictive of Poor Prognosis in Multiple Sclerosis

Factor	Evidence	Reference
Demographics		
Gender (poor prognosis associated with male sex)	Mixed	19,115,116
Age at onset (older associated with rapid progression)	Strong	19,20,117,118
Age at onset (young age confers poor long-term prognosis)	Strong	16,119
Race (African Americans associated with rapid progression)	Strong	31,120,121
Symptoms at Onset		
EDSS score	Mixed	14,19,122
Motor symptoms	Mixed	10,19
Sensory symptoms	No association	19–21,123
Optic neuritis (linked to benign course)	Mixed	19,21,118
Sphincter symptoms	Strong	10,19,21
Brainstem symptoms	Mixed	19,117,118,124
Cerebellar symptoms	Mixed	19,118,124
Vascular co-morbidities	Limited	125
Mental symptoms	Limited	126
Cognitive impairment in benign MS	Limited	27
Early Disease Outcomes		
Incomplete recovery from first attack	Strong	10,19,117,124
Short interval between first and second attack	Strong	19–21
Early relapse frequency	Mixed	10,117
Magnetic Resonance Imaging Assessment		
Volume of T1 hypointense lesions	Mixed	127
Number of T2 lesions	Mixed; strong early in disease but weak later	128–131
Volume of T2 lesions	Strong	6,127
Location of T2 lesions	Limited	48
Rate of lesion growth	Limited	6
Number of Barkhof criteria fulfilled	Mixed	128,130,132
Number of Gd enhancing lesions	Mixed	60,130
Brain volume	Mixed	127,133
Grey matter hypointensity	Limited	54,55,134
Spinal cord lesions	Limited (CIS progression to MS)	52,135

CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis.

investigated. Recent studies of paediatric-onset and adult MS have shown that among those with established MS, individuals with lower vitamin D levels have a higher risk of subsequent relapse.[40,41]

An Italian study showed that cognitive assessment may predict disease course in benign MS. People who failed more than two cognitive tests were 20 % more likely to progress over five years (hazard ratio [HR]=1.4; 95 % confidence interval [CI] 1.1–1.7; p=0.003).[27] Early cognitive impairment may be associated with cortical thinning and thus indicative of a more aggressive disseminated cortical disease. Cognitive impairment has also been found to be a predictor for conversion from CIS to MS.[42]

Magnetic Resonance Imaging and Other Imaging Modalities

MRI is an established tool for monitoring disease activity and relapse in MS, providing an objective and quantitative measurement of disease pathology. The classical MRI predictors have been brain volume changes, T2 lesion volume and count of gadolinium (Gd)-enhancing lesions. A recent meta-analysis of 19 randomised studies of patients with RRMS found significant correlations between the treatment effect on MRI lesions and EDSS worsening.[43] Studies have, however, given mixed results and are summarised in *Table 1*.

In a 20-year study (n=107), T2 lesion volume and its changes at early time-points have been found to correlate with disability after 20 years. Abnormal MRI findings at baseline were predictive for conversion of CIS to clinically definite MS. Furthermore, T2 lesion volume increases for at least 20 years in RRMS and the rate of lesion growth was three-times higher in those who developed SPMS than in those who remained in RRMS.[6] Another study found a linear correlation between T2 levels and EDSS score at lower EDSS levels.[44]

Other studies have suggested that conventional MRI measures have insufficient sensitivity and specificity to reveal the true degree of pathological changes occurring in MS.[45,46] MRI is still considered the most sensitive test to predict conversion from CIS to definite MS.[47]

Localisation of MRI lesions may be significant; recent findings suggest that the spatial distribution of T2 lesions is relevant in predicting the risk of long-term progression in primary progressive MS (PPMS). In particular, lesions localised to the motor and associative tracts at baseline correlated with a more rapid clinical progression over time.[48] Lesion location is also predictive of disability; infratentorial lesions have been associated with a high risk for earlier occurrence of relevant disability.[49] Using a lesion probability mapping approach, brain regions have been identified where the presence of MS lesions predicts an early need for bilateral walking support.[50]

Similarly, spinal cord localisation tends to be associated with a poor prognosis.[51] A recent study found that the presence of asymptomatic spinal cord lesions is associated with a substantial risk for clinical conversion from radiologically isolated syndrome to either an acute or progressive event; this risk is independent of brain lesions on MRI.[52] The lesion distribution may also be used to predict specific symptoms (for example, spinal cord lesions confer a greater risk of bladder and bowel impairment, although the association is weak).[53]

While correlations have been observed between lesion localisation and prognosis, there are shortcomings to these studies. The EDSS and other scales based on a standard neurological examination that are often employed to measure disability and progression tend to focus on motor functions versus cognitive impairments. As such, it is not surprising that lesions within motor control areas and the spinal cord will result in greater disability as predicted by these tests. It may therefore be more appropriate and accurate to use global measures such as atrophy or to include more cognitive measures.

More powerful MRI predictors are emerging, such as grey matter involvement in MS.[54] Grey matter T2-hypointensity resulting from excessive iron deposition has been associated with worsening disability in patients with MS.[55] Bermel et al. found that grey matter T2-hypointensity predicted the progression of brain atrophy in patients given placebo, but not in patients treated with interferon beta (IFNβ)-1a.[56] Grey matter volume was a stronger predictor of physical and cognitive impairment than white matter volume.[57] Subtraction MRI imaging is a rapidly emerging technique that may be combined with conventional MRI outcomes as a sensitive predictor of disease progression in MS.[58]

Advances in MRI technology may also improve its predictive power; high-field strength MRI scans are more sensitive than the 1.5T instruments currently used in clinical practice. High-field scanners at magnetic strengths of up to 7T and higher in research settings can generate images at higher resolution, resulting in an increase in the number and volume of lesions detected compared with 1.5T images.[59] In one study, scans detected multiple, discrete cortical lesions at 8T, whereas none were seen on 1.5T images.[60,61] Scans at 3T have been shown to correlate better with clinical status in MS than scans at 1.5T.[62]

Newer techniques are emerging that may provide prognostic information but require further validation. Brain magnetisation transfer imaging (MTI) is relatively easy to perform, although quite difficult to standardise, and provides a measure of lesion burden in MS.[63] A reduction in magnetisation transfer ratio (MTR) represents a lowered exchange of protons within the tissue upon imaging and may be associated with demyelination, macrophage infiltration, or axon damage.[64] The technique is sensitive to brain tissue changes over one year in early PPMS and may provide information on short-term clinical prognosis in early PPMS.[65] The technique has also been used to demonstrate the association between grey matter damage and long-term disability in MS.[66] A method that could automatically determine brain atrophy as brain parenchymal fraction (BPF) was recently presented and could offer a way to apply quantitative measures of disease progression in clinical practice.[67]

Deep grey matter lesions have been detected by transcranial sonography (TCS) in patients with MS and an association found with a higher rate of disease progression.[68] Measurement of brain metabolites using magnetic resonance spectroscopy (MRS) may be a useful prognostic technique in combination with conventional MRI.[69] The techniques involved in MRS are labour-intensive which limits its use in everyday clinical practice, although MRS findings correlate well with clinical disability in RRMS.[70]

Retinal nerve fibre atrophy and macular volume determined by optical coherence tomography (OCT) have been found to correlate

with neurodegeneration in MS and may be potentially useful predictors.[71] However, additional research is necessary before OCT can be considered a reliable measure of disability or marker of disease progression.

In summary, the predictive power of MRI and other imaging techniques is increasing, and new outcome measures are providing alternative means of determining neurodegenerative changes. With further validation and clinician experience, these new technologies should ultimately prove to be valuable tools to determine treatment responses and prognosis.

Biomarkers of Disease Progression

Several biomarkers have been described that are indicative of neuronal, axonal and glial loss such as neurofilaments and tau. These are summarised in *Table 2*.[72–74] However, the majority of research in biomarker development in MS has been concerned with monitoring disease activity and thus so far not yielded biomarkers that predict disease development or disease course. There is a need for validation of potential biomarkers. In recent years, many antibodies have been hailed as possible biomarkers only to be found not to be reliable in further clinical testing.[75–78] Recently, an antibody against a potassium channel expressed in the CNS was described in about 50 % of patients with MS and in less than 1 % in the control groups.[79] It is thus possible that this antibody may confer a specific marker for a subset of patients with MS but need further confirmation before firm conclusions may be made.

Neurofilament proteins have been detected in the cerebrospinal fluid (CSF) and blood samples of MS patients and have recently emerged as one of the most promising potential biomarkers of disease progression in MS.[80] An association has been found between neurofilament light (NFL) levels in CSF in early MS and disease severity at long-term follow-up (8–20 years).[81] Furthermore, treatment with natalizumab normalised the level of neurofilament in the CSF in one study indicating this protein as a possible marker for treatment response.[82]

The presence of oligoclonal immunoglobulin G (IgG) bands (OCBs) may be a sensitive predictor of conversion from CIS to a definite diagnosis of MS.[83,84] Although it has not yet been used to predict disease course, it may have the potential to direct therapeutic decisions. The significance of IgG OCBs is controversial; while some studies claim that the absence of IgG OCBs correlates to a slower progression of disability,[85] others suggest that the OCBs alone do not predict disease course.[86,87] Problems with the laboratory testing of OCBs have been described by Rauchway et al., who found that of 225 US labs assessed, only 61 (27 %) were performing the OCB test according to consensus conference recommendations.[88]

Other promising biomarkers include microRNAs (miRNAs), short non-coding RNAs with the potential to serve as biomarkers for different human diseases, most notably cancer. Recent studies have identified specific miRNAs that are associated with MS.[89] The best single miRNA marker, hsa-miR-145, differentiated RRMS patients from healthy controls with a specificity of 89.5 %, a sensitivity of 90.0 % and an accuracy of 89.7 %.[89,90] Proteomic studies have also identified several potential biomarkers[91] including chitinase 3-like 1 (CHI3L1) which is being investigated as a biomarker in a number of inflammatory conditions. Elevated levels of CHI3L1 have been associated with conversion of CIS to clinically definite MS[92] and was recently found in the plasma of patients with progressive forms of MS.[93]

Table 2: Biomarkers and their Potential Clinical Use in Multiple Sclerosis

Biomarker	Potential Clinical Use	Reference
Cytokines		
Interleukin 10 in CSF	Possibly predicts response to IFNβ	136
Th1/Th2 cytokines	Predictive of response to GA	96
Proteins		
Neurofilament proteins in CSF	May predict disease severity and response to treatment	80–82
Tau in CSF	May predict neurodegeneration but evidence mixed	137–139
Antibodies		
NAbs to IFNβ	Predictive of reduced clinical activity to IFNβ	99
NAbs to natalizumab	Preductive of reduced clinical activity to natalizumab	102
Genes and Gene Expression		
GPR3	Expressed at significantly low levels in those with high disease activity	107
IL17RC	Expressed at significantly low levels in those with high disease activity	107
HLA-DRB1	Underrepresented in those with poor long-term outcomes	108

CSF = cerebrospinal fluid; GA = glatiramer acetate; IFNβ = interferon beta; NAbs = neutralising antibody; Th1/Th2 = T-helper 1/T-helper 2.

Biomarkers may also be useful in predicting response to MS therapies. Interleukin-17F (IL-17F) was posited as a promising marker in patients with MS treated with IFNβ,[94] however, a subsequent replication study has cast doubt on the future utility of IL-17 as a predictive biomarker.[95] Recent studies have found that patterns of T-helper 1/T-helper 2 (Th1/Th2) cytokines may predict clinical response in MS patients treated with glatiramer acetate (GA).[96] When treating patients with natalizumab the presence of the John Cunningham (JC) virus is associated with a risk of developing progressive multifocal leukoencephalopathy.[97]

Neutralising antibody (NAb) titres also have a predictive role: NAbs have been associated with reduced clinical activity of IFNβ[98–101] and natalizumab.[102] The American Academy of Neurology recommends discontinuation of IFNβ in cases of sustained high NAb titres.[103]

Overall, the area of biomarkers is promising, but studies remain poorly validated and as yet there is no single serum or CSF-based marker that predicts prognosis in MS. It may be necessary to redress the research bias towards the discovery of new therapeutic agents, and focus greater effort on clinical validation.

Gene Expression Profiling

Gene expression profiling has become important in recent years in determining MS risk.[104] An optimal set of 29 genes has been defined as a clinical outcome predictive gene expression signature and appropriately classified 88.9 % of patients.[105] A two-stage predictor to time of next relapse in MS based on gene expression was recently developed. The first-stage predictor was based on the expression levels of 10 genes, and predicted the time to next relapse with a resolution of 500 days (error rate=0.079, $p<0.001$). If the next relapse was predicted to occur within 500 days, a second-stage predictor

based on an additional set of nine genes was used to estimate the time to next relapse with greater accuracy (resolution of 50 days). The error rate of the second-stage predictor was 2.3-fold lower than the error rate of random predictions (error rate=0.35, p<0.001).[106]

Of 110 genes that have been proposed as predictive biomarkers, most could not be confirmed in a study of patients (n=148) with good and poor disease courses.[107] However, the guanine nucleotide-binding (G) protein-coupled membrane receptor gene *GPR3* was expressed at significantly lower levels in patients with poor disease progression. The *GPR3* gene therefore has a high potential to be a biomarker for predicting future disease activity. In addition, the IL-17 cytokines receptor gene *IL-17RC* was identified as a new and promising transcript-based biomarker candidate.[107] Genotyping sets of MS patients with good and poor long-term outcomes showed that the *HLA-DRB1*01* gene was significantly underrepresented in those with poor long-term outcomes.[108] Gene expression profiling may also reveal biomarkers that predict response to therapy.[109,110] Despite the many advances in genetics and gene expression profiling, they are currently not very practical in the clinical setting and may continue to have limited value in the future.

Composite Score of Multiple Sclerosis Prediction

Clearly, no single factor is predictive of MS progression, which has led to research to develop a composite scoring tool to predict the clinical course of MS at diagnosis. Initial studies of the MS Functional Composite (MSFC), based on a test of walking speed, hand dexterity and cognitive function, suggested that this could predict the level of disability and extent of brain atrophy progression in patients with RRMS.[111] However, subsequent studies suggest that it has minimal predictive power.[14]

The Bayesian Risk Estimate for MS (BREMS) score was developed to predict the risk of reaching SPMS. It was based on a number of clinical factors including type of onset, motor and sphincter relapses, and an early increase in disability. In a study of 1,245 patients, among the patients with higher BREMS scores, 29 % reached SPMS within 10 years of disease onset while only 4 % of those with a lower BREMS score reached SPMS (relative risk [RR] 6.5 [95 % CI 2.8–14.8]). Kaplan–Meier curves confirmed that a higher BREMS value was significantly related to a higher risk of developing SPMS (p<0.0001).[112]

Other composite scores have been developed using variables such as clinical and MRI factors, IgM and IgG OCBs and quantitative IgM and IgG determination. These models have been validated in small sample cohorts.[23,113]

Composite MRI measures may also provide a useful predictive tool. A recent study described a Magnetic Resonance Disease Severity Scale (MRDSS), which encompassed three equally weighted whole brain MRI measures of lesions and atrophy: T2 hyperintense lesion volume, the ratio of T1 (hypointense) to T2 lesion volume and normalised whole brain volume. However, the MRDSS gave only modest improvements in predicting the risk of developing sustained progression of physical disability three years later compared with other metrics.[114] No spinal cord scans are included in the measurement of the MRDSS, although cord lesions and atrophy are probably closely associated.

The development of composite scores is an active and promising area of research but none has yet gained widespread use and it is possible that these scores may prove to be too complicated to be clinically useful. Further studies validating these measures are therefore warranted.

Summary and Future Directions

Treatment of MS requires a multidisciplinary approach and patient involvement in treatment decisions. In current medical practice, physicians are faced with the difficult task of identifying patients who they feel present with more or less severe MS based on groupings of clinical features. The lack of clear prognostic indicators tips medicine from a science towards more of an art form, practiced by MS physicians who must use their experience and knowledge to guide therapy decisions and decide individual MS patient treatment plans. Using predictive factors to direct treatment in MS is a considerable challenge; while many clinical, imaging, biochemical and genetic factors appear to show value as prognostic indicators in MS, there is a need for further validation of these techniques. Clinical features such as numbness, weakness and incoordination are much too insensitive for following disease course and, more importantly, are largely subjective and not quantitative.

The progress in developing MRI techniques and the attempts to establish reliable and quantitative measures have been somewhat disappointing thus far. There remains no universal method that can be implemented in routine clinical practice and expanded to larger cohorts in real life. In the future, quantitative measurements of brain activity with MRI and validated biochemical biomarkers are likely to become more important and accepted in predicting disease activity, disability and progression than clinical parameters. It is necessary to focus efforts on obtaining objective and reliable measurements that are automated and easy to use. Biochemical markers sensitive in detecting inflammation and nerve damage would complement present MRI techniques.

A major limitation of studies to date is the fact that they relate to groups of individuals. Ultimately, individual predictors are needed, which presents a much more challenging issue. It may be possible in the future to create computerised models that allow physicians to input unique variables such as age, gender, race, MRI parameters and cellular or biochemical factors in order to guide therapeutic decisions. ■

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