From progression to progress: The future of multiple sclerosis

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ABSTRACT

Significant advances have been made in the diagnosis and treatment of multiple sclerosis in recent years yet challenges remain. The current classification of MS phenotypes according to disease activity and progression, for example, does not adequately reflect the underlying pathophysiological mechanisms that may be acting in an individual with MS at different time points. Thus, there is a need for clinicians to transition to a management approach based on the underlying pathophysiological mechanisms that drive disability in MS. A Canadian expert panel convened in January 2023 to discuss priorities for clinical discovery and scientific exploration that would help advance the field. Five key areas of focus included: identifying a mechanism-based disease classification system; developing biomarkers (imaging, fluid, digital) to identify pathologic processes; implementing a data-driven approach to integrate genetic/environmental risk factors, clinical findings, imaging and biomarker data, and patient-reported outcomes to better characterize the many factors associated with disability progression; utilizing precision-based treatment strategies to target different disease processes; and potentially preventing disease through Epstein-Barr virus (EBV) vaccination, counselling about environmental risk factors (e.g. obesity, exercise, vitamin D/sun exposure, smoking) and other measures. Many of the tools needed to meet these needs are currently available. Further work is required to validate emerging biomarkers and tailor treatment strategies to the needs of individual patients. The hope is that a more complete view of the individual's pathobiology will enable clinicians to usher in an era of truly personalized medicine, in which more informed treatment decisions throughout the disease course achieve better long-term outcomes.

KEYWORDS: Multiple sclerosis, pathophysiology, disease progression, fluid biomarker, digital biomarker

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Introduction

Multiple sclerosis is a chronic neurodegenerative disorder of the central nervous system (CNS) in which inflammation and progressive neuroaxonal injury contribute to physical and cognitive disability. Significant advances over the past 3 decades have included the introduction of disease-modifying therapies (DMT)[1]; the characterization of relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS) phenotypes[2]; the introduction of newly-modified diagnostic criteria for MS, clinically-isolated syndrome (CIS) and radiologically-isolated syndrome (RIS)[3]; and the increasingly sophisticated use of imaging and laboratory evaluations to investigate the underlying immunohistopathology of MS.[4]

Despite these successes, there remain substantial shortfalls in our understanding of MS. While genetic, environmental and patient factors play a role in MS onset and the development of neurodegeneration, the etiology of the disease remains unknown. There are no clinical/radiological factors or biomarkers that can accurately predict clinical outcomes in individual patients. Moreover, while numerous DMTs have been introduced to control the dysregulated inflammatory response seen in MS, their impact on neurodegeneration and disability progression is inconsistent.[5]

These limitations illustrate the need to shift research and treatment away from an approach rooted in clinical observation to one that is based on the interaction and evolution of underlying disease mechanisms in individual patients, as recently suggested by the International Advisory Committee on Clinical Trials in Multiple Sclerosis.[6]

To address this issue, an expert panel of MS clinicians and researchers convened in January 2023 to discuss the key developments that are needed to advance the field of MS. While the 5 steps outlined below are aspirational, each is firmly grounded on the path of current research and may serve to chart the course for improving patient outcomes in the years ahead.

Shift focus to a disease mechanism-based approach

MS has traditionally been viewed as a disease initially driven by neuroinflammatory processes (as is seen in RRMS) in which an

accumulation of neuroaxonal damage progresses to a secondary neurodegenerative phase (as observed in SPMS). With progression from the outset (PPMS), there was a similar evolution but with the relapsing-remitting phase seen as 'amputated'.[7] This classification of MS aided clinical research and enabled greater uniformity of patients enrolled in clinical trials, but did not adequately reflect the pathobiological aspects of the disease. It is now apparent that the spectrum of MS phenotypes represents a single disease entity, and that inflammation and neurodegeneration are present to varying degrees from the outset. An MS prodrome has been described that may suggest early immunopathological or neurodegenerative changes.[8] To this may be added the observation of early brain atrophy and imaging evidence of chronic, active lesions reflective of central-nervous system compartmentalized inflammation in individuals with radiologically isolated syndrome (RIS), and elevated levels of neurofilament-light chain (NfL), a biomarker of neuroaxonal damage, 6 years prior to an MS diagnosis.[9,10]

Thus, inflammation and neurodegeneration are evident at the earliest stages of the disease process and act in concert, rather than sequentially. The pathophysiological processes contributing to neuroaxonal loss have been reviewed elsewhere,[6,11] but 3 key mechanisms can be briefly summarized.

- **Acute inflammation**, characterized by the invasion of activated lymphocytes and monocytes across a semi-permeable blood-brain barrier, and adaptive and innate immune cell activation in the CNS. This results in the formation of focal white-matter lesions, demyelination and neuroaxonal damage.
- **Diffuse compartmentalized inflammation within the central nervous system**, in which non-resolving inflammation promotes widespread activation of microglia and astrocytes that is associated with tissue damage and remodelling. Chronic active lesions may accumulate iron from phagocytes at the lesion edge and contribute to demyelination, axonal transection and Wallerian degeneration and are associated with earlier physical and cognitive disability.[12] Diffuse meningeal inflammation may organize in tertiary lymphoid structures that are associated with cortical demyelination and neuronal loss, possibly due to the release of cytotoxic factors.[13,14]
- **Demyelination and axonal loss.** Inflammation directed at myelin antigens and bystander inflammation result in demyelination, which leads to redistribution of sodium ion channels, an accumulation of calcium ions and proteolytic degradation of the axon.[15,16] Important to this process is oxidative stress, which impairs the trafficking and function of mitochondria and which in turn is exacerbated by mitochondrial failure. Oxidative stress directly damages neurons and oligodendrocytes and interferes with differentiation of oligodendrocyte precursor cells (OPC).[17] An accelerated accumulation of tissue loss in the brain and spinal cord is a major determinant of disability progression.[18,19]

While remyelination can restore function in the earlier stages of MS, poor clearance of myelin debris, the release of toxic mediators by microglia and astrocytes, and impaired OPC function contribute to remyelination failure.[20,21]

Genetic and/or environmental factors are associated with the development and subsequent disease course of MS, dysregulated immune activation and demyelination/remyelination. These include genetic risk variants,[22,23] Epstein-Barr (EBV) virus infection,[24] low sun exposure/low vitamin D levels,[25] childhood obesity,[26] smoking,[27] dysbiosis in the gut microbiome,[28] and immunosenescence,[29,30] among others. These risk factors likely interact in varying ways throughout the disease course to produce a highly individualized pathophysiological process in which specific mechanisms assume greater or lesser prominence. This would account for the differences in disease onset, phenotypic expression and clinical course seen in persons with MS (PwMS).

As such, the current classification of MS phenotypes according to disease activity and progression[31] does not adequately reflect the underlying pathophysiological mechanisms that may be acting in an individual PwMS at different time points. But there are emerging approaches that may facilitate better classification of MS phenotypes in the future. One recent study used machine learning to identify 3 MS subtypes based on temporal changes in thirteen MRI features (grey-matter volume, white-matter lesion volume, T1/T2 ratios in different brain regions).[32] MRI subtypes were more strongly associated with the risk of disability progression than clinical phenotypes, suggesting that MRI findings more closely reflected the underlying pathology. A separate study used multi-omics factor analysis to identify 3 MS subtypes based on glial gene expression and oligodendrocyte composition.[33] Such models could be further refined to incorporate additional MRI, clinical and laboratory findings to achieve what has been termed 'precision phenotyping'[34] that could enable a prognosis and treatment plan specific to the individual PwMS.

Develop and validate disease-specific biomarkers

Disease-specific biomarkers have the potential to identify the unique pathobiological signature in individual patients so as to refine the prognosis and guide treatment decisions. Such an approach would necessarily incorporate multiple markers indicating the extent and severity of acute and diffuse inflammation, demyelination and axonal loss, and response to interventions at different stages of the disease process.[6] Further refinements could be obtained with the addition of genetic profiling and biomarkers of environmental factors that influence progression.

At present, only MRI measures (baseline T2-hyperintense lesion count and the development of new/enlarging T2 lesions

over time) are widely used for prognosis and treatment decision-making.[35] There are a number of emerging MRI techniques that have the ability to measure components of CNS-compartmentalized, chronic inflammation that current MRI techniques cannot capture. These include iron-sensitive MRI sequences that can detect rims of microglia activation around chronic lesions[36,37]; the detection of cortical lesions[38]; and contrast-enhanced fluid-attenuated inversion recovery (FLAIR) imaging of leptomeningeal inflammation that may reflect cortical demyelination.[39] Other research methods that may further characterize CNS pathology include PET imaging using radioligands specific to activated microglia and astroycytes, such as 18-kDa translocator protein (TSPO)[40]; magnetic transfer imaging (MTI) to evaluate myelin content[41]; magnetic resonance spectroscopy (MRS) to evaluate metabolic changes associated with neuroaxonal loss and mitochondrial dysfunction[42]; and diffusion tensor imaging, which examines microstructural changes, including axonal and myelin loss in the brain and spinal cord.[43] Although most of these techniques have demonstrated robust correlations with clinical disability in pwMS, a major hurdle preventing their widespread use in clinical practice is the lack of access to necessary sequences, software for image processing, determining clinically-relevant thresholds, and integration into the clinical workflow.

Of emerging importance is optical coherence tomography (OCT), a relatively inexpensive method of detecting thinning of the retinal nerve fibre layer (RNFL) and ganglion cell layer-inner plexiform layer (GCL-IPL) as a biomarker of brain and spinal-cord atrophy.[44,45] Eye-movement impairments in MS are associated with grey-matter atrophy and cognitive impairment,[46] and novel tracking devices and digital tools are now in development to provide a simple, non-invasive assessment of disease progression.[47,48]

Numerous fluid biomarkers have been investigated in MS (reviewed in[49]). One of the more studied is neurofilament-light chain (NfL), an axonal cytoskeleton protein and a proposed biomarker of axonal injury in MS and other conditions. NfL levels in cerebrospinal fluid and serum are elevated prior to MS onset and remain elevated at diagnosis.[9,50] Higher baseline NfL levels are prognostic of worse physical and cognitive outcomes,[51] and a reduction in NfL is associated with a treatment response in relapsing MS.[52,53] Some centres have started to employ NfL testing as a biomarker for prognosis and clinical response. However, its utility in individual patients and in progressive MS, as with other proposed biomarkers, requires further investigation.

While NfL primarily reflects inflammatory insult to axons in MS, glial fibrillary acidic protein (GFAP) is a marker of astrocyte activity that may provide insights about glial involvement in diffuse white matter damage that is occurring independently of neuroinflammation.[54] As such, it may be a better marker of progression independent of inflammation, a process that predominates in the later stages of MS.

It should be noted, however, that a single biomarker is unlikely to be sufficiently informative of the complex pathobiology of MS. Efforts are now being made to use multiple fluid biomarkers to ascertain the predominant disease mechanisms and provide a more finely-grained image of individual disease phenotypes. NfL and GFAP can differentiate PwMS with acute disease activity from those at risk of progression.[55] Similarly, analysis of NfL with chitinase-3 like-protein-1 (CHI3L1), a marker of gliosis, has been used to identify PwMS with active disease at risk of disability progression.[56] Elevated GFAP and triggering receptor expressed on myeloid cells-2 (TREM2), a marker of microglial activation, correlate with neuronal cell death in progressive MS.[57] NfL has also been used as part of a biomarker panel to differentiate MS subgroups according to inflammatory and neurodegenerative markers; the panel comprised NfL, the matrix protein osteopontin, the B cell chemoattractant CXCL13, and the macrophage/microglia marker CD163.[58] Future efforts will likely involve combining fluid, imaging, and digital biomarkers as prognostic and disease-monitoring tools in clinical practice. While the ideal constituents of a biomarker panel have not been determined, such an approach could overcome some of the deficiencies of individual biomarkers and provide a more complete view of the underlying pathobiology.

Adopt a data-driven approach

For a more fully integrated assessment of disease activity throughout the clinical course, laboratory measures would ideally be used in conjunction with imaging (MRI, OCT) and digital biomarkers, and applied based on accumulating evidence (Figure 1). Research on the use of physiological and behavioural data with digital devices (e.g. smart phones, wearable devices, eye-tracking technology) is in its infancy (reviewed in[59]). But these data sources have the potential to provide real-time and ongoing evaluations of multiple domains (e.g. gait, upper and lower motor function, brainstem function, visual acuity, cognition) that could be integrated with laboratory, imaging and patient-reported outcome (PRO) results to enable greater precision in patient management. Validation of digital biomarkers is ongoing.[60,61] Preliminary studies have shown that smart phone-based assessments correlate with clinical disability and MRI outcomes[48] and accurately estimate EDSS scores.[62] Additional work is needed to address issues concerning data collection and interpretation, use in clinical practice and patient privacy.

A multimodal approach to data collection was adopted for the Canadian Prospective Cohort Study to Understand Progression in MS (CanProCo).[63] The ongoing multicentre study is integrating clinical findings, conventional and advanced MRI, and laboratory results (blood, CSF, RNA sequencing) with data obtained from questionnaires, smartphones (e.g. upper limb function, gait, cognition, mood) and iPad (e.g. Multiple Sclerosis Performance Test[64]) applications. The goal is to identify more sensitive tools to detect subtle worsening in physical and cognitive function and to better characterize the many factors associated with disability progression.

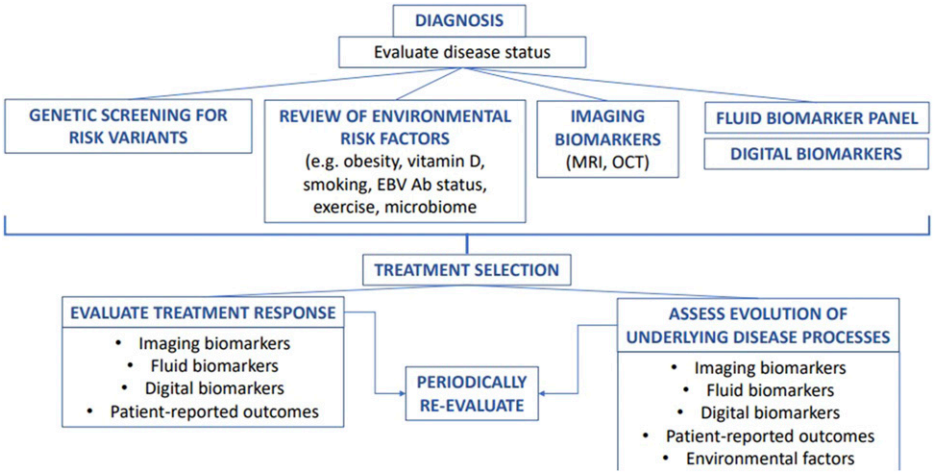

Figure 1. Multimodal approach to personalized medicine at different stages of the MS disease process.

The future of personalized medicine will require multiple treatment strategies

Clinical practice is currently guided by "big data" findings obtained from clinical trials and database analyses, which are not sufficiently prognostic of the clinical course or predictive of treatment response in individual patients. As noted above, the development of a battery of laboratory, imaging and digital biomarkers would enable clinicians to determine which pathological mechanisms were predominant at different stages of the disease process in an individual PwMS and tailor a treatment plan that would more precisely target those disease factors. More widespread use of PROs would further enable a more personalized approach to clinical management.

At present, DMTs are primarily useful during the inflammatory phase of MS. What is needed are novel treatments that target the neurodegenerative processes of non-resolving inflammation, demyelination, oxidative damage and ion channelopathy, and promote remyelination and axonal survival. A number of promising therapies are now in development. Bruton's tyrosine kinase (BTK) inhibitors (e.g. evobrutinib, tolebrutinib, fenebrutinib, remibrutinib and orelabrutinib) modulate B cell and macrophage/microglia activity and may have effects on CNS-compartmentalized chronic inflammation that current DMTs are not able to adequately control. Phase II trials reported a reduction in gadolinium-enhancing lesions.[65,66] Preclinical studies demonstrate that BTK inhibition decreases B cell activation, meningeal inflammation, and activation of pro-inflammatory microglia.[67-69] Moreover, exploratory analyses have demonstrated that higher doses of evobrutinib and tolebrutinib reduce slowly-expanding lesion (SEL) volumes in comparison to lower doses, suggesting there may be an effect of these drugs on chronic active lesions.[70,71] Another tyrosine kinase inhibitor, masitinib, inhibits microglia and mast cell activity and was shown to slow disability progression in a phase III trial.[72] Alpha-lipoic acid is a potent antioxidant and may inhibit lymphocyte migration across the BBB; a pilot study found a modest effect on walking performance in progressive MS.[73] Several repurposed drugs, such as the antidiabetic agent metformin and the antimalarial hydroxychloroquine, have pleiotropic effects in the CNS that may reduce axonal damage and promote remyelination.[74,75] Clemastine has been shown to have remyelinating potential both in preclinical studies and in a small Phase II trial of MS.[76]

In employing a treatment strategy that targets multiple disease mechanisms, individual agents may not be fully effective on conventional endpoints but may still have a place in therapy. Drug and non-drug therapies could be used either serially or in combination at different times in the clinical course or in individual patients in whom selected disease mechanisms have been shown to predominate. This could also enable a change in how clinical trials are performed. At present, clinical and imaging surrogate endpoints (relapses, new MRI lesions) are not highly predictive of long-term outcomes. The use of an array of validated disease biomarkers (laboratory, imaging, digital and PROs) could greatly accelerate drug development and lead to a new generation of more precisely targeted therapies.

Prevent MS in at-risk populations

The recent findings that EBV infection substantially increased the risk of developing MS, and that neuroaxonal degeneration, as assessed by serum NfL, was only present after seroconversion, suggest that EBV is an important trigger of MS.[24] A number of mechanisms linking EBV with MS have been proposed, such as cross-reactivity of EBV and myelin antigens or CNS molecules such as GlialCAM (molecular mimicry), or the accumulation of EBV-infected B cells in the CNS promoting the survival of autoreactive T cells (reviewed in[77]). It is likely that several mechanisms are involved (reviewed in[78]). Interestingly, the onset of neurodegenerative changes occurring 5-10 years prior to diagnosis[9] roughly coincides with the development of an MS prodrome of neuropsychiatric and cognitive impairment.[79]

These data raise the possibility that EBV vaccination in seronegative children and adolescents could prevent the development of MS. Several EBV vaccines are currently in development. A phase II trial of a prophylactic vaccine did not achieve sterilizing immunity but was effective in preventing infectious mononucleosis,[80] an MS risk factor,[81] which may be sufficient to prevent MS onset. New mRNA vaccine technology may enable the development of more effective vaccines and is currently being examined in the ECLIPSE trial (NCT05164094).

Eradication of EBV in seropositive individuals or PwMS may not be achievable. Use of antiviral therapy may be preferred to mitigate ongoing virus-associated activity. The proof of principle is interferon-β, an MS therapy that may act in part by reducing the T cell proliferative response to Epstein-Barr nuclear antigen 1 (EBNA1).[82] Antiviral studies to date have been underpowered but have reported modest improvements in clinical and MRI endpoints.[83,84] An antiviral 'cocktail', as used in AIDS/HIV, or in combination with other therapies or at certain times in the disease process, may be a more effective approach. An example is the antiviral tenofovir, which inhibits lytic EBV reactivation, which has been proposed in combination with anti-CD20 therapy.[78] Another approach is autologous EBV-specific T cell therapy, which reported promising results in progressive MS.[85]

Additional efforts are needed to further refine MS risk scores based on the interaction of known genetic risk alleles and environmental factors.[86] There is also the potential to intervene in individuals with 1 or more modifiable risk factors, such as low sun exposure/low serum 25(OH)D, adolescent obesity and smoking (reviewed in[87]). Exercise has immunomodulatory effects and may be recommended both for MS prophylaxis and as an adjunct to treatment (reviewed in[88,89]). A Mendelian randomization analysis of genetic/environmental factors found that reducing obesity, increasing physical activity and raising serum 25(OH)D levels could reduce the risk of developing MS.[90]

Conclusions

The significant progress seen in MS management over the past 2 decades is the prelude to the coming era of truly personalized medicine for PwMS. All areas of medicine evolve from clinical observation and anecdotal reports to a research-based understanding of the etiology and pathophysiology of disease. Over the past decade, MS has begun such a transition with the recognition of the complex pathobiological mechanisms that contribute to demyelination and neuroaxonal loss and which results in neurological disease worsening.

A great deal more work is needed to understand the etiology and pathogenesis of the underlying mechanisms of disease in MS and how they interact. This is a major task but many of the tools are at hand in the form of fluid, imaging and digital biomarkers, all of which will need to be improved, validated and shown to be applicable at the level of the individual patient. A second task would be to coordinate and integrate laboratory, imaging and digital data so as to construct a more complete picture of an individual's MS throughout the disease course. Access to advanced clinical tools and their integration into clinical workflow are important practical aspects that will need to be taken into account before any of these novel techniques can be widely utilized in clinical practice. Artificial intelligence (AI) techniques have successfully employed imaging and laboratory findings to improve diagnostic accuracy.[91] The next step would be to use AI to integrate clinical, biomarker and patient-related data to construct a 'digital twin' as a guide to a personalized treatment plan.[92]

A more complete view of the individual's pathobiology would enable clinicians to make more informed treatment decisions to achieve better long-term outcomes. The treatment plan would involve the initiation of oneone or more therapies based on the patient's predominant disease mechanisms at a specific time point, and adapt treatment strategies as needed based on ongoing biomarker-based measures of treatment response and disease evolution.

Many steps will be needed in the clinician's proverbial thousand-mile journey of better understanding an individual's disease process and designing an optimal treatment plan. That process can begin now with more widespread adoption of existing tools (e.g. NfL, PROs) in clinical practice. Progress thereafter will be incremental as new tools are developed. But the first steps can and should be taken on the path of personalized medicine for PwMS.

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Author contributions

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