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Time to reconsider the classification of multiple sclerosis

Multiple sclerosis is an inflammatory demyelinating disease of the CNS, showing various clinical manifestations depending on the site, nature, and extent of the inflammatory lesions. In practice, multiple sclerosis is classified into clinical subtypes—relapsing-remitting, primary progressive, and secondary progressive—on the basis of the patient's clinical course. Since the turn of the century, the precise distinction between relapsing-remitting and secondary progressive multiple sclerosis has become important, because secondary progressive disease does not respond to most disease-modifying drugs approved for relapsing-remitting disease (although disability progression in people with secondary progressive multiple sclerosis can be slowed with siponimod). However, the boundary between relapsing-remitting and secondary progressive disease is often unclear, and diagnosis of secondary progressive multiple sclerosis tends to be delayed because progression typically takes place silently without accompanying relapses (referred to as progression independent of relapse) in these patients.[1] Furthermore, it has become obvious that the traditional multiple sclerosis subtypes do not represent the biological heterogeneity of patients, as shown by their heterogeneous microglia gene expression profiles.[2] Research has explored how to group patients with multiple sclerosis according to objective markers that might represent radiological, immunological, or neurodegenerative processes. Taken together, in their Personal View in *The Lancet Neurology*, Tanja Kuhlmann and colleagues have good reasons to propose the need for a new mechanism-driven framework to define multiple sclerosis progression.[3] Although the goal is distant and many obstacles might arise (such as reaching a consensus between physicians, academia, and stakeholders), the time seems right to launch initiatives to reframe the classification of multiple sclerosis subtypes.

Although there are many potential players in the pathogenesis of multiple sclerosis, including B cells, helper T cells, cytotoxic T cells, and microglia, the traditional framework for multiple sclerosis subtypes is indifferent to the pathogenesis. The new framework should reflect the biological mechanisms of disease that are instructive for treatment of patients with diverse backgrounds. I hope that the new classification will be also helpful for early diagnosis of secondary progressive disease or perhaps of a new subtype of multiple sclerosis that is not responsive to drugs approved for relapsing-remitting disease, so that these drugs are not given to patients unnecessarily.

Kuhlmann and colleagues[3] discuss pathological mechanisms of multiple sclerosis progression and then provide an overview of the advances in neuroimaging in the past 10 years that enable estimation of the neuropathological changes in clinical practice. They provide a list of radiological tools to measure progressive activity of multiple sclerosis, which should be useful in both clinical practice and clinical trials. Furthermore, they note that genetic factors can influence pathology,[4] indicating that the eventual new subtype definition might also rely on genetic factors.

Given the increased numbers of measures to evaluate the pathology of multiple sclerosis, many new subgroups of the disease might be proposed. The subgroups might be classified by machine learning,[5] and artificial intelligence or other technologies might be useful in solving the issue of complexity if there are numerous potential subgroups. However, the practical value of new platforms for identifying patients in the different subgroups will need to be validated by independent research teams.

Although it is not the focus of the Personal View,[3] immunology might be a driving force in creation of a new classification of multiple sclerosis. Studies have revealed that the brains of patients with secondary progressive multiple sclerosis are infiltrated with tissue-resident CD8 memory T cells[6] and cytotoxic CD4 T cells.[7] Numbers of cytotoxic CD4 T cells expressing eomesodermin (EOMES), a transcription factor expressed by cytotoxic T cells and natural killer cells, are increased in the peripheral blood of patients with multiple sclerosis, and are dominant among diffusely infiltrating CD4 T cells in patients' brains.[7] As such, by using immunological parameters, patients with relapsing-remitting disease might be differentiated from those with secondary progressive disease,[7] suggesting that blood biomarkers that reflect brain pathology are worth exploring further.

Many genetic and environmental factors can influence the clinical course of multiple sclerosis, with evidence that environmental factors and lifestyle can promote

or prevent development and progression. The gut microbiome structure and numbers of particular bacterial species and strains, which are potentially influenced by diet, could play a substantial role in the development of multiple sclerosis. Numbers of bacteria producing short-chain fatty acids are reduced in the gut of patients with relapsing-remitting multiple sclerosis, compared with healthy people not diagnosed with multiple sclerosis.[8,9] Moreover, patients with secondary progressive disease have different gut bacterial species and metabolomic profiles than patients who have relapsing-remitting disease,[9] which might add a further dimension to the new classification.

Note that the history-based classification of multiple sclerosis into relapsing-remitting, primary progressive, and secondary progressive forms is widely supported, as it is simple and can be used globally, without requiring any special measurements. An example of a reasonably simple and practical framework for evaluation of multiple sclerosis involves the discovery of anti-AQP-4 autoantibodies, a biomarker of neuromyelitis optica spectrum disorder, which has drastically changed the management of patients who come to hospitals with concerns about onset of multiple sclerosis or neuromyelitis optica. These antibodies are not only a diagnostic marker, but also a biomarker guiding selection of drugs.[10] In patients with multiple sclerosis, biomarkers such as NF-L should help us to evaluate the neurodegenerative components of multiple sclerosis pathology. Although the available measures for assessing progression of multiple sclerosis (such as NF-L) are valuable in conducting clinical research and clinical trials, their value in management of individual patients remains unclear. I anticipate that identification of new biomarkers might open a new era in the classification of multiple sclerosis.

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