

“A rose by any other name”: does defining extreme phenotypes add to the management of multiple sclerosis?

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by recurrent episodes of neurological dysfunction. Diagnostic criteria have evolved over time but the core principles of “dissemination in time” and “dissemination in space” have been retained. Different clinical phenotypes are recognized, such as the commonly encountered relapsing remitting and secondary progressive forms of the disease. Less commonly patients may present with a progressive course from onset.

Schee and Viswanathan describe a cohort of patients with short segment relapsing myelitis clinically and radiologically indistinguishable from myelitis associated with MS (1). The patients did not fulfil the recently published McDonald criteria for the diagnosis of MS (2) as lesions were restricted to the spinal cord and patients did not develop cerebral or optic nerve lesions or “dissemination in space”. The updated criteria allow the substitution of juxtacortical lesions for cortical lesions; however, standard MRI has limited ability to detect cortical lesions, which if detected would potentially have allowed a diagnosis of MS to be confirmed. When the McDonald criteria for the diagnosis of MS are strictly applied, they are highly specific but may lack sensitivity. Although these patients with recurrent short segment myelitis may have failed to fulfill diagnostic criteria, the authors argue that the patients described may represent a distinct but restricted phenotype of MS.

The patients described share many features with other MS patients: partial myelitis characterized by peripheral instead of central cord lesions; presence of oligoclonal

bands in cerebrospinal fluid; attacks with moderate severity but good recovery; response to MS disease modifying therapies; and a progressive course in some. Others have also described patient cohorts, which might be considered limited or restricted forms of MS and argued that they may be variant MS phenotypes, including progressive solitary sclerosis (3), a progressive syndrome otherwise indistinguishable from progressive forms of MS but with only a single demonstrable lesion; and radiographically isolated syndrome (4), MRI findings which are strongly suggestive of MS lesions with absence of neurological symptoms. Despite the restricted clinical phenotypes, these cohorts may share the same fundamental pathophysiology as classical MS and may benefit from appropriate MS preventative strategies.

In contrast, inflammatory demyelinating disorders, such as neuromyelitis optica spectrum disorder (NMOSD) and likely myelin oligodendrocyte glycoprotein (MOG)-associated diseases, which satisfy MS diagnostic criteria (5) and were once considered part of the spectrum of MS, are now accepted as distinct entities. While they may share overlapping features, they are distinguishable from MS by their distinctive relapses (e.g., severe myelitis, intractable vomiting and hiccup and eating disorders) (5), neuroradiology (e.g., longitudinally extensive cord lesions) (5), poor recovery, different response to preventative treatments (6), pathology (e.g., loss of aquaporin-4 (AQP4) immunoreactivity in lesions of NMOSD) (7), and highly specific biomarkers [e.g.,

AQP4-IgG (8) and MOG-IgG (9)]. The biology of these inflammatory demyelinating disorders is fundamentally distinct from MS with direct implications for disease management. Preventative strategies that are proven effective in MS may actually worsen AQP4-IgG and MOG-IgG associated inflammatory demyelinating disorders and the distinction is vitally important (10-12).

Recognizing that these restricted clinical phenotypes may be part of the MS spectrum despite failing to meet formal diagnostic criteria is important. As described in this article, these patients had a relapsing phenotype and benefited from MS disease modifying therapies in controlling the frequency of relapses. Some of the reported patients later developed a progressive myelopathy. When MS patients develop progression, it is typically presents as a progressive myelopathy and gait impairment. Patients may develop cervical cord atrophy secondary to prior inflammatory spinal cord lesions. Initiating MS disease modifying therapies early may prevent or delay later disability (13). Without a diagnosis of MS, patients may be unable to access appropriate preventative medications.

However, dissection of MS into many phenotypes based on restricted involvement at a given point of time may have limited value. The phenotype may evolve with time with more attacks, and our ability to distinguish subclinical involvement elsewhere in the CNS is limited, but constantly evolving with new technologies. The strategy may not accomplish what was accomplished with NMOSD, namely identification of novel diseases with distinct immunobiology and need for different treatments.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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