ARE MS AND NMO TWO POLARIZED DISEASES? DOES THIS HAVE TREATMENT IMPLICATIONS? – YES

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Although the clinical manifestations of multiple sclerosis (MS) and neuromyelitis optica (NMO) overlap, the long held suspicion that they are distinct diseases is now established beyond a reasonable doubt. However, the features that truly distinguish NMO from MS are quite different from those historically cited as the basis of their distinctness. Originally, the characteristics that were used to define NMO from MS was its monophasic course and clinical manifestations restricted to optic nerve and spinal cord.

Neuromyelitis optica was wrongly assumed to be a monophasic disease. It is now clear that it is usually a relapsing condition, as is MS. Furthermore, the restriction of involvement to optic nerve and spinal cord, although partly true, is no longer regarded as an absolute distinguishing feature. It is not unusual for NMO to affect the brain, but when it does, it usually does so in a qualitatively and quantitatively different way than MS. While NMO and MS may not distinguishable based on the characteristics of brain lesions for each individual patient, groups of patients and the majority of individuals with NMO differ from those from MS based on the frequency and location of brain lesions. For example, cortical lesions are not detectable radiologically or pathologically in NMO, whereas they are commonly detectable in MS. Lesions of MS tend to surround microvessels, whereas they do not in MS. Brain lesions in NMO have an unusual predilection for periependymal regions and circumventricular organs, including the area postrema and the hypothalamus. They key differences between NMO and MS are relative rather than absolute: the relative predilection for optic nerve and spinal cord attacks, the greater severity of attacks, and the specific radiological characteristics of NMO (especially longitudinally extensive spinal cord lesions). Perhaps the most specific clinicoradiological characteristic that does distinguish these conditions is the presence of a longitudinally extensive (spanning 3 spinal segments or longer) T2 signal abnormality in the context of an acute myelitis; this is present in the vast majority of cases of NMO, and hardly ever in MS, at least not in adults.

Most specifically, the presence of aquaporin-4 (AQP4) autoantibodies, first reported by Lennon et al in 2004, and the marked loss of immunoreactive AQP4 accompanied by astrocyte-specific pathological changes in active lesions, are characteristics that distinguish between NMO and MS.

The underlying cause of MS and NMO remain unknown. The identity of the antigenic target is unknown in MS, but appears to be AQP4 NMO. AQP4-reactive T-cells are identifiable in patients with NMO, as are AQP4-specific B cell clones in CSF and AQP4-reactive antibodies in serum. The immune system has a number of markers of Th17 polarization in NMO. Th17 polarization has also been reported in MS, although the pathology of NMO lesions is more suggestive of Th17 immunopathology (resembling Th17-polarized experimental allergic encephalomyelitis) than is MS. None of these issues of potential overlap and unresolved issues regarding pathogenesis changes the conclusions that must be reached about their distinctness mentioned previously.

It has long been appreciated that MS immunomodulatory therapies, especially interferon beta and glatiramer acetate, were ineffective in NMO. More recently, it was found that a majority of those patients experiencing severe attacks following administration of interferon beta for MS were subsequently found to have NMO rather than prototypic MS. Furthermore, other MS immunomodulatory therapies are likely less than optically effective or potentially deleterious to patients with NMO, including natalizumab. Plasma exchange is an example of a treatment that is effective across a wide spectrum of inflammatory demyelinating diseases, including prototypic MS, likely because there is an important component of antibody-mediated contribution in at least some patients with MS, as well as in patients with NMO. However, plasma exchange seems to be particularly effective in NMO, despite the greater severity of attacks in this condition, which is negatively associated with favorable response. Similarly, rituximab seems to be effective in both conditions.

Thus, while a comprehensive understanding of both conditions, MS and NMO, remains elusive, emerging information about the clinical, radiological, immunological, pathological and therapeutic aspects of these conditions favors the hypothesis that they are distinct and "polarized" diseases and that their differences have therapeutic consequences.