● **PERSPECTIVE**

Multiple sclerosis and neuromyelitis optica spectrum disorders: some similarities in two distinct diseases

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic inflammatory disorder of the central nervous system that particularly involves the optic nerve and spinal cord. It is pathologically characterized by astrocytopathy, followed by tissue destruction (Fujihara, 2011). Historically, NMOSD has been considered to be an Asian optic-spinal form of multiple sclerosis (MS), as patients with NMOSD were distributed predominantly in Asian rather than in Western countries.

Highly sensitive and specific NMO-specific immunoglobulins (NMO-IgGs) that target aquaporin 4 (AQP4) have been discovered in patients with NMOSD. This led to NMOSD being considered as a separate clinical entity from MS. Moreover, the finding that interferon (IFN)-β, widely used and proven effective in patients with MS, sometimes exacerbates NMOSD (Papadopoulos et al. 2014), further led to this distinction. Additionally, new generation drugs including fingolimod and natalizumab are also known to exacerbate NMOSD (Papadopoulos et al. 2014), suggesting that the distinction between MS and NMOSD is critical in determining appropriate therapy.

Although MS and NMOSD are essentially distinct diseases, recent studies have shown similarities. To reduce the misdiagnosis, it is crucial to know not only the differences but also the similarities between these two diseases. In this article, we focus on the similarities between MS and NMOSD and discuss the association between these overlaps and disease pathogenesis, from pathological, radiological, and immunological perspectives.

Pathological characteristics of MS and NMOSD: The characteristics of MS lesions have been well defined, and although heterogeneous, they can be classified into 4 types (Lucchinetti et al. 2001): Pattern I and II lesions are characterized by active demyelination, associated with a T cell- and macrophage-dominated inflammation. The distinguishing feature of pattern II lesions is the prominent deposition of Igs and complements. Pattern III shows diffusely spread demyelination with prominent loss of myelin-associated glycoprotein in association with oligodendrocyte apoptosis. Pattern IV lesions also present with demyelination, accompanied by oligodendrocyte death. Thus, demyelination is a key feature of MS lesions.

On the other hand, NMOSD lesions classically present with complement deposition, granulocyte infiltration, and astrocyte necrosis, which lead to global tissue destruction (Fujihara, 2011). However, Misu et al. (2013) described that NMOSD lesions are highly heterogeneous and can be categorized into 6 different types according to pathological analyses. Lesions of type 1, 2, and 3 reflect the typical NMOSD lesions described previously. These lesions are followed by demyelination, leading to global tissue destruction, accompanied by Wallerian degeneration. Type 4 and 5 lesions are characterized by clasmatodendrosis of astrocytes, in the absence of complement activation. Interestingly, type 6 lesions are characterized by primary demyelination in association with oligodendrocyte apoptosis and astrocytic clasmatodendrosis, which is similar to a pattern III lesion in patients with MS. Moreover, the authors observed that type 6 lesions were seen in 4 of 7 patients with NMOSD, suggesting that type 6 lesions are common in patients with NMOSD.

Radiological characteristics of MS and NMOSD: Magnetic resonance imaging (MRI) studies also revealed apparent similarities between MS and NMOSD. Although longitudinally extensive transverse myelitis lesions are considered characteristic features of NMOSD (Fujihara, 2011), short myelitis was found in 14% of the initial myelitis occurrences among 25 patients with NMOSD positive for anti-AQP4 antibodies, and 40% of those patients presented with short myelitis at first manifestation (Flanagan et al., 2015). These observations suggest that short myelitis episodes may not be uncommon among NMOSD patients with anti-AQP4 antibodies and that NMOSD cannot be distinguished from MS based only on a single spinal cord MRI finding. Recently, we reported that spinal cord ring enhancement (RE) was common not only in patients with MS, but also in patients with NMOSD in the active phase, with a frequency of 31.2% (Yokote et al., 2015). These similarities raised some doubt about whether spinal cord lesions with RE in NMOSD were completely distinct from those in MS.

Recent studies using dynamic MRI demonstrated that, at the very early stage, RE was likely to be small and nodular and expands centrifugally. Then, at about day 5, enhancement became larger and expanded centripetally in a ring-like fashion, as the blood-brain barrier (BBB) of the peripheral veins began to open, and the BBB of the central veins began to close (Gaitán et al., 2011). Although not statistically significant, the duration from disease onset to detection of spinal cord lesions with RE on MRI tended to be longer than that in spinal cord lesions without RE (Yokote et al. 2015), suggesting that timing of MRI scans could be associated with RE formation. This would not fit with the concept of a typical NMOSD pathology, which includes severe astrocytic destruction, because it would be impossible that the BBB of central veins with severe astrocytic damage could close again several days after the occurrence. In addition, we found that myelin basic protein levels in the cerebrospinal fluid (CSF) of patients with NMOSD with spinal cord RE were higher than in patients with NMOSD without spinal cord RE, suggesting that RE is associated with more severe myelin damage (Yokote et al., 2015). Considering that typical NMOSD lesions are characterized by marked AQP4 loss, while myelin remains relatively preserved (Fujihara, 2011), elevated MBP levels in the CSF do not match typical NMOSD pathology. Moreover, a CSF biomarker study has shown that CSF-MBP levels in patients with NMOSD are comparable with those in patients with MS, whereas CSF-GFAP levels in NMOSD were much higher than in those with MS (Fujihara, 2011); this also suggested that astrocytic damage should be considered the main pathology in typical NMOSD. Therefore, we propose that higher CSF MBP levels, in association with spinal cord RE, may suggest primary demyelination, which is indicative of a type 6 lesion, although more CSF markers, including GFAP, need to be analyzed for confirm our hypothesis.

Intriguingly, we also found that male sex was significantly associated with spinal cord RE (Yokote et al., 2015). NMOSD predominantly affects women (Fujihara, 2011); this predominance may support the idea that spinal cord lesions with RE could be distinct from "typical" NMOSD lesions that are classified as types 1, 2, and 3.

Immunological characteristics of MS and NMOSD: Another similarity between MS and NMOSD is the cytokine profile. Although MS has been classically considered to be a T helper (Th) 1–associated disease, recent studies demonstrated that interleukin (IL)-17 plays a pivotal role in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) in mouse models of MS. In humans, the frequency of Th17 cells in the CSF of patients with MS was significantly higher than that of patients with noninflammatory neurological disease (Brucklacher-Waldert et al., 2009). Moreover, the number of Th17 cells

in the CSF increases significantly during MS exacerbation but that of Th1 cells does not (Brucklacher-Waldert et al., 2009). These findings strongly suggest that IL-17 plays a pivotal role in the pathogenesis of MS. However, in the same study, the absolute number of Th1 cells both in the blood and the CSF was about 10-fold higher than the number of Th17 cells, further indicating that Th1 cells are the key players in MS. In patients with NMOSD, Th17- and Th2-related cytokines are increased in the CSF as well as in the serum, as compared with patients with MS, suggesting that Th17 cells are mainly involved (Uzawa et al., 2014). Based on these data, it is likely that "typical" MS is immunologically distinct from NMOSD.

Interestingly, however, Axtell et al. (2010) described that a subset of patients with relapsing-remitting MS (RRMS) had high serum concentrations of the Th17 cytokine IL-17F. Cluster analysis of the cytokine profiles grouped 6 non-responders to interferon (IFN)-β; these individuals had significantly higher serum concentrations of IL-17F than the responders. The authors hypothesized that non-responders to IFN-β had aggressive Th17-mediated disease that is very similar to NMOSD, as NMOSD is probably a Th17-driven disease and is known to be exacerbated by administration of IFN-β.

Similarly, we previously showed that serum amyloid A (SAA) levels were increased in patients with NMOSD, as well as in those with "atypical" MS (Yokote et al., 2013). SAA has been recognized as a critical mediator of disease pathogenesis, owing to its capacity to promote expression of Th17-related cytokines. Here, we showed that SAA levels were evenly elevated in patients with NMOSD, but varied greatly in patients with RRMS. These results were concordant with the concept that MS was immunologically heterogeneous. Furthermore, RRMS patients with high SAA levels presented an atypical phenotype, with smaller T2 lesion volumes on brain MRI, similar to those found in NMOSD (Yokote et al., 2013). This observation suggested that the cytokine balance varies in patients with MS and that some groups of patients with MS have both a cytokine balance and clinical phenotype similar to patients with NMOSD. This may be due to differences in the ability to traffic to distinct sites within the central nervous system between Th1 and Th17 cells.

Conclusions: As discussed in preceding sections, there are some similarities between MS and NMOSD, although these 2 diseases are essentially distinct (**Figure 1**). Understanding the similarities between MS and NMOSD helps us to see an atypical case that is the borderline between MS and NMOSD. It is essential to choose carefully an appropriate treatment based on the nature of the lesion and the pathophysiological background: IFN-β should be avoided for this borderline patient at least since the disease can be mediated by Th17.
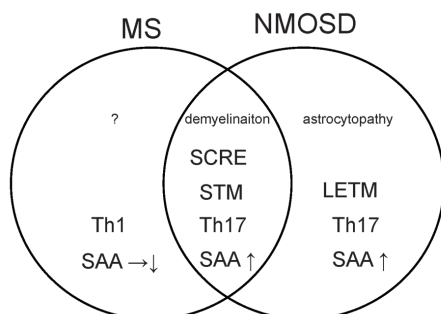
Figure 1 Similar and distinct features of multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSDs).
There are several common characteristics between MS and NMOSD, although these are essentially distinct diseases. LETM: Longitudinally extensive transverse myelitis; SPRE: spinal cord ring enhancement; SAA: serum amyloid A; STM: short transverse myelitis; Th: T helper.

What explains these similarities? One of the possible keys to answering this question could involve the heterogeneity of MS and NMOSD. It is possible that "immunological heterogeneity" exists between MS and a subset of patients with MS, which could immunologically resemble NMOSD rather than "typical" MS. In NMOSD, clinical as well as pathological findings are diverse, even in NMOSD with anti-AQP4 antibodies, which is thought to be a relatively uniform disease. The immunological and pathological background of each patient should be considered regardless of whether the patient is diagnosed as having MS or NMOSD.

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References

Axtell RC, de Jong BA, Boniface K, van der Voort LF, Bhat R, De Sarno P, Naves R, Han M, Zhong F, Castellanos JG, Mair R, Christakos A, Kolkowitz I, Katz L, Killestein J, Polman CH, de Waal Malefyt R, Steinman L, Raman C (2010) T helper type 1 and 17 cells determine efficacy of interferon-beta in multiple sclerosis and experimental encephalomyelitis. Nat Med 16:406-412.

Brucklacher-Waldert V, Stuerner K, Kolster M, Wolthausen J, Tolosa E (2009) Phenotypical and functional characterization of T helper 17 cells in multiple sclerosis. Brain 132:3329-3341.

Flanagan EP, Weinshenker BG, Krecke KN, Lennon VA, Lucchinetti CF, McKeon A, Wingerchuk DM, Shuster EA, Jiao Y, Horta ES, Pittock SJ (2015) Short myelitis lesions in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorders. JAMA Neurol 72:81-87.

Fujihara K (2011) Neuromyelitis optica and astrocytic damage in its pathogenesis. J Neurol Sci 306:183-187.

Gaitán MI, Shea CD, Evangelou IE, Stone RD, Fenton KM, Bielekova B, Massacesi L, Reich DS (2011) Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions. Ann Neurol. 70:22-29.

Lucchinetti CF, Bruck W, Parisi JE, Scheithauter B, Rodriguez M, Lassmann H (2001) Heterogenity of multiple sclerosis lesions: implication for the pathogenesis of demyelination. Ann Neurol 47:707-717.

Misu T, Höftberger R, Fujihara K, Wimmer I, Takai Y, Nishiyama S, Nakashima I, Konno H, Bradl M, Garzuly F, Itoyama Y, Aoki M, Lassmann H (2013) Presence of six different lesion types suggests diverse mechanisms of tissue injury in neuromyelitis optica. Acta Neuropathol 125:815-827.

Papadopoulos MC, Bennett JL, Verkman AS (2014) Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. Nat Rev Neurol 10:493-506.

Uzawa A, Masahiro M, Kuwabara S (2014) Cytokines and chemokines in neuromyelitis optica: Pathogenetic and therapeutic implications. Brain Pathol 24:67-73.

Yokote H, Nose Y, Ishibashi S, Tanaka K, Takahashi T, Fujihara K, Yokota T, Mizusawa H (2015) Spinal cord ring enhancement in patients with neuromyelitis optica. Acta Neurol Scand. 132:37-41.

Yokote H, Yagi Y, Watanabe Y, Amino T, Kamata T, Mizusawa H (2013) Serum amyloid A level is increased in neuromyelitis optica and atypical multiple sclerosis with smaller T2 lesion volume in brain MRI. J Neuroimmunol 259:92-95.