Imaging biomarkers in Multiple sclerosis and neuromyelitis optica spectrum disorder

김 남 희
동국의대

Nam-Hee Kim, MD, PhD
Department of Neurology, Dongguk University Ilsan Hospital

Multiple sclerosis (MS) is an autoimmune inflammatory disorder of the central nervous system (CNS) in which different environmental factors act on the basis of a multi-genetic trait. It is characterized by focal demyelinating plaques and widespread neurodegeneration throughout the white and gray matter. Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune astrocytopathy that mainly involves the optic nerve and spinal cord. The identification of the aquaporin-4 (AQP4) antibody has helped to facilitate differentiation of NMOSD from MS. The clinical signs are similar to those of MS, with the result that it is often difficult to differentiate, thus leading to misdiagnosis. As the treatment and prognosis of NMOSD and MS are different, it is important to make an accurate and early diagnosis of NMOSD.
Visual impairment appears to be prominent in both disorders. Optic neuritis (ON) is typically more severe, recurrent, and frequently bilateral in NMOSD compared to MS. Optical coherence tomography (OCT) is a non-invasive imaging tool that has been used in MS and NMOSD to quantify damage to the retina, including the ganglion cells and their axons. OCT represents a surrogate marker of neuro-axonal integrity in the visual pathway, which might be useful in differentiating NMOSD from MS and serve as an outcome parameter in clinical studies.
Structural magnetic resonance imaging (MRI) can be used to obtain anatomical information about the CNS and to quantify evolving pathology in MS and NMOSD. These imaging techniques can help identify important differences between MS and NMOSD such as disease-specific damage.
This review focuses on the current knowledge of the role as surrogate biomarker of OCT and MRI in patients with MS and NMOSD.

Key word : Multiple sclerosis, Neuromyelitis optica spectrum disorder, Optical coherence tomography, Biomarker

Introduction

The exact pathophysiological mechanisms behind MS and NMOSD have still not been fully elucidated.[1,2] However axonal degeneration in addition to demyelination has recently been considered more relevant in MS, which has been documented in both active and inactive lesions, distal to the areas affected by autoimmune inflammation, and early in the disease course.[3,4] Conversely, the pathophysiology in NMOSD predominantly involves the deposition of IgG and complement, resulting in a loss of AQP4 proteins on astrocytes and severe neuronal and axonal loss.[5] Recent years have brought a rapid evolution of diagnostic imaging studies including OCT and MRI in the field of demyelinating disorders.[1,2,3,4]

1. Optical coherence tomography (OCT)

OCT practically measure the thickness of peripapillary retinal nerve fiber layers (RNFL) (Figure 1 and 2). The fact that these retinal nerve fibers are the only unmyelinated axons within the central nervous system renders the afferent visual pathway an ideal model for studying axonal and neuronal degeneration in MS and NMOSD.[6] OCT represents a surrogate marker of neuro-axonal integrity in the afferent visual pathway.[2]

The damage seen in eyes without a history of optic neuritis is likely due to subclinical disease activity, which is commonly identified in MS but has only recently been reported in NMOSD.[7,8] It is possible that in NMOSD, Müller cells (which span the entire thickness of the retina and

contain an abundance of AQP4 channels) may be affected in patients without ON history, although this remains unconfirmed.[7,8] Ganglion cell layer (GCL) and inner plexiform layer (IPL) thinning have been observed in both MS and NMOSD; in particular, NMOSD patients typically exhibit thinner GCL and IPL compared to MS patients, most

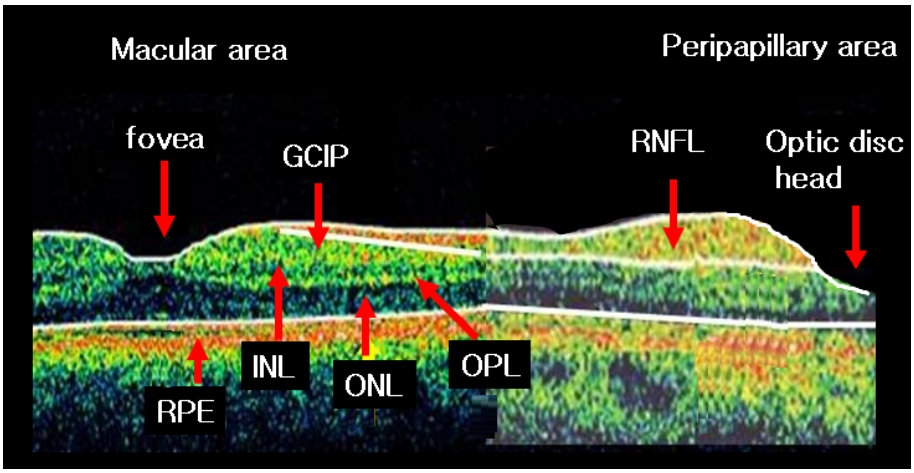
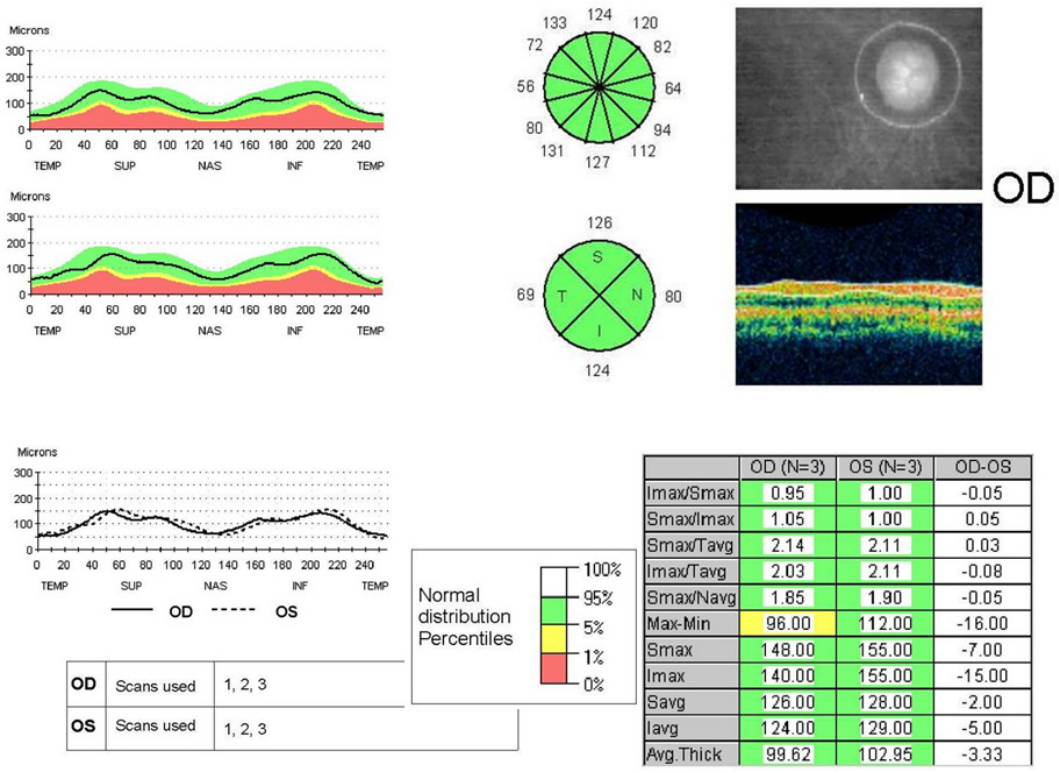


Figure 1. Image from OCT scan demonstrating the retinal architecture. Cell layers are labeled as follows: INL=inner nuclear layer; GCIP=ganglion cell and inner plexiform layer; RNFL = retinal nerve fiber layer; RPE = retinal pigment epithelium; ONL= outer nuclear layer; OPL = outer plexiform layer.



	OD (N=3)	OS (N=3)	OD-OS
Imax/Smax	0.95	1.00	-0.05
Smax/Imax	1.05	1.00	0.05
Smax/Tavg	2.14	2.11	0.03
Imax/Tavg	2.03	2.11	-0.08
Smax/Navg	1.85	1.90	-0.05
Max-Min	96.00	112.00	-16.00
Smax	148.00	155.00	-7.00
Imax	140.00	155.00	-15.00
Savg	126.00	128.00	-2.00
Iavg	124.00	129.00	-5.00
Avg.Thick	99.62	102.95	-3.33

Figure 2. Peripapillary OCT scan. Right lower table presents the thickness of retinal nerve fiber layer.

likely reflecting more severe neuronal and axonal involvement in NMOSD.[6,9,10] Inner nuclear layer (INL) thickening has been observed more frequently and seems to have the potential to differentiate between MS and NMOSD.[2,11] INL thickening is often associated with microcystic macular edema (MME).[2,11]

The meta-analysis presented that the RNFL loss was more severe in NMOSD than in MS; however, subclinical axonal damage was also found in eyes without optic neuritis in NMOSD.[11] The inter-eye RNFL difference between eyes with or without optic neuritis was more prominent in NMOSD (−30.98 μm) than in MS (−9.87 μm).[11] The RNFL loss was more severe in NMOSD than in MS, and the inter-eye RNFL difference between eyes with or without optic neuritis, which may be useful in differentiating NMOSD from MS.[2,11] Numerous studies demonstrated that optic neuritis in NMOSD typically results in more severe thinning of RNFL and GCL and more frequent development of MME than in MS.[2,3,6,10-13] OCT might be useful in differentiating NMOSD from MS and serve as an outcome biomarker in clinical studies.

2. Magnetic resonance image (MRI)

Conventional imaging techniques are commonly used to monitor disease activity by quantifying lesion load (lesion number and volume) and, more recently, neurodegeneration, through the measurement of global brain volume loss, frequently referred to as brain atrophy.[2]

Brain volume loss can be assessed either cross-sectionally, using brain parenchymal fraction (BPF), or longitudinally, using registration-based approaches such as SIENA (Structural Image Evaluation, using Normalization, of Atrophy).[2]

While lesion detection and qualitative assessments with conventional imaging techniques are used in clinical practice for diagnosis and monitoring, this approach lacks pathological specificity and is therefore unsuitable for characterizing the biological mechanisms and temporal sequences underlying inflammatory demyelination and neuro-axonal degeneration in MS and NMOSD.[1,2]

Advanced MRI techniques may provide a more quantitative and potentially more sensitive tool to detect subtle changes in the normal appearing white or gray matter (NAWM/NAGM), which are often undetectable by conventional MRI sequences.[1,2,4]

Nevertheless, both conventional and advanced MRI techniques can provide complementary information.[1] Multimodal imaging at high and ultra-high magnetic field strengths is yielding biologically relevant insights into the pathophysiology of blood–brain barrier dynamics and both active and chronic inflammation, as well as mechanisms of lesion healing and remyelination.[1,2,4]

Using diffusion tensor imaging (DTI), widespread occult damage was demonstrated in the NAWM of NMOSD.[14] However, the NAWM was less affected in NMOSD than it was in MS; specifically, the axonal injuries and diffusion abnormalities in the association fibers were more severe in MS than they were in NMOSD.[14]

Gray matter imaging biomarkers can be used to distinguish NMO from MS and may facilitate the differential diagnosis in clinical practice.[15] There is cross-sectional and longitudinal evidence of diffusely distributed neurodegenerative surrogates in the MS group (including thalamic atrophy, cervical cord atrophy and progressive widespread diffusion and myelin water imaging abnormalities in NAWM) but not in NMOSD, where localized abnormalities in the optic radiations of those with severe visual impairment were noted.[15]

NMOSD showed predominately spinal cord atrophy with mild brain atrophy, while MS demonstrated more brain atrophy, especially in the gray matter. Mean upper cervical cord area is the main MRI derived parameter for explaining clinical disability in NMOSD and MS, and may serve as a potential biomarker for further clinical trials, especially in NMOSD.[1,16,17] In addition, between relapses, there were no new silent brain lesions in the NMOSD group. These findings indicate that global CNS neurodegeneration is not a feature of NMOSD.[1,16,17]

Acknowledgment of NMOSD imaging patterns and their mimicry of disorders has been crucial in supporting early NMOSD diagnosis, especially for unusual clinical manifestations of this demyelinating disease.[18-20]

The followings summarized distinctive imaging features of optic neuritis, myelitis, and brain lesions in demyelinating disorders such as AQP4-IgG–positive NMOSD versus MOG-IgG–positive NMOSD and MS.[18,21]

AQP4-IgG–positive patients preferentially present with long-length, bilateral and posterior optic nerve involvement with chiasmatic extension. MOG-IgG–positive patients usually exhibit long-length, bilateral, and anterior optic nerve involvement, with intraorbital optic nerve swelling and usually with perineural gadolinium enhancement.[5,18,21] MS patients classically have unilateral and short-length optic neuritis.[18,17] AQP4-IgG–positive patients have more longitudinal extensive transverse myelitis that is centrally or both centrally and peripherally located and involves more than 50% of the cord area, predominantly in the cervicothoracic region. MOG-IgG–positive patients usually have medullary conus and thoracolumbar spinal cord involvement with an atypical appearance on axial views but commonly centrally or both centrally and peripherally located.[18,21] MS patients have longitudinal short-length spinal cord lesions, particularly in the cervical segment, which are peripherally distributed on axial images in the dorsal and lateral areas.[18,19]

AQP4-IgG–positive patients typically have periventricular and circumventricular involvement and involvement of the corticospinal tracts (focal or associated with vasogenic edema, demonstrating a trident-shaped appearance).[5,18,19] MOG-IgG–positive patients more often have basal ganglia, thalamic, and infratentorial lesions.[18-21] MS patients typically have ovoid white matter lesions that are distributed in the periventricular regions (Dawson fingers), corpus callosum, callosal-septal interface, cortical/juxtacortical areas, and infratentorial regions with involvement of the intrapontine trigeminal nerve.[5,18] Unlike in MS, NMOSD was previously thought to feature no brain involvement; however, it is now well-established that development of nonspecific brain lesions can also occur in NMOSD.[18,19]

Since clinical and radiological features sometimes overlap between demyelinating disorders, future studies to identify novel imaging biomarkers for differentiating disorders are still needed.

Conclusion

Emphasis was placed on points that MRI and OCT are used as imaging biomarkers to differentiate these diseases. In the past few decades, advances have been made toward better understanding of NMOSD. Since the identification of an NMOSD-specific biomarker, new and typical MRI and OCT patterns have been added. However, the increased number of imaging findings has widened the list of differential diagnosis for demyelinating disorders. The imaging biomarkers of NMOSD and MS could aid in the differential and precise diagnosis and figure out the in vivo pathology of these demyelinating disorders.

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