

# Foveal thinning in neuromyelitis optica

## A sign of retinal astrocytopathy?

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Patients with neuromyelitis optica spectrum disorder (NMOSD) typically manifest recurrent episodes of optic neuritis (ON) and myelitis. Recently revised diagnostic criteria<sup>1</sup> do not restrict the diagnosis of NMOSD to patients associated with elevation of anti-aquaporin 4 antibody (AQP4Ab), capable of causing destruction of astrocytes expressing AQP4. If compatible clinical and radiologic features are present, the diagnosis of NMOSD is given to patients with autoantibodies (Ab) specific for myelin oligodendrocyte glycoprotein (MOG).<sup>2</sup> However, compared with MOGAb+ NMOSD, clinical relapses tend to be more serious in AQP4Ab+ patients and could result in devastating neurologic sequelae manifested by blindness, paralysis, cognitive dysfunction, or neurogenic pain.

While acute relapses are characteristic of the relapsing-remitting form of MS, insidious worsening related to chronic neuroinflammation is the basis for the diagnosis of secondary progressive MS. Although secondary progressive disease was assumed to be uncommon in NMOSD,<sup>3</sup> recent studies relying on MRI findings have described progressive brain or spinal cord atrophy<sup>4,5</sup> without a sign of relapses in patients with AQP4Ab+ NMOSD.

In this issue of *Neurology*<sup>®</sup> *Neuroimmunology & Neuroinflammation*, Oertel et al.<sup>6</sup> measured the foveal thickness and the thickness of surrounding structures (peripapillary retinal nerve fiber layer and ganglion cell and inner plexiform layers) in patients with NMOSD using optical coherence tomography (OCT). They compared eyes from patients who had long extensive spinal cord lesions archetypal for NMOSD but no history of ON with eyes from NMOSD patients with history of ON and eyes from healthy controls. In parallel, diffusion tensor imaging (DTI) was used to evaluate the microstructural changes in the optic radiation, which is responsible for transmitting visual signals from the retina to the visual cortex. The authors demonstrate that central foveal thickness is significantly reduced in the eyes of

the 6 patients without a history of ON as compared to controls, although high-contrast visual acuity of these patients was normal. Fovea is a tiny pit in the macula of the retina and is responsible for the central, high-resolution color vision. As the fovea is enriched in Müller cells expressing AQP4, their observation suggests the occurrence of primary retinal astrocytopathy in NMOSD. DTI analysis also showed secondary microstructural changes in the afferent visual system in parallel with the foveal thinning. Shortly before this publication,<sup>6</sup> OCT was applied by Korean and Japanese groups for the analysis of retinal changes in patients with NMOSD.<sup>7,8</sup> Notably, the Korean study also showed the presence of foveal thinning in the retina of unaffected eyes of patients with NMOSD. Moreover, the foveal thinning was correlated with a reduction in low-contrast visual acuity in the Korean study, implying that the retina of the “unaffected eyes” in AQP4Ab+ NMOSD might be actually damaged by chronic autoimmune inflammation targeting Müller cells or retinal astrocytes.

One could say that prevention of relapses is a goal of therapy for NMOSD, assuming that only serious relapses are thought to cause neurologic sequelae. However, the presence of retinal changes without previous ON indicates that an insidious development of pathology cannot be ignored in patients with NMOSD. Given that the life expectancy of patients with NMOSD has substantially improved, the future goal of therapy should not only be prevention of relapses, but prevention of new lesion development by immunotherapy under close monitoring. Alterations in Müller cells have been also described in a rodent model of NMOSD.<sup>9</sup> This pathology was dependent on both AQP4Ab and T cells, indicating the importance of T-cell control to achieve good control of NMOSD.

It is known that the shape and size of retinal fovea evaluated by OCT differ among different ethnic

### See article

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groups. In this regard, data from both Caucasian and Asian patients are precious and useful. The size of the avascular area in the fovea may influence OCT evaluation.<sup>10</sup> Therefore, future studies should evaluate the avascular area as well.

The study by Oertel et al.<sup>6</sup> together with recent publications from other investigators<sup>7,8</sup> have begun to stimulate discussion about the goal of therapy in patients with NMOSD regarding the prognosis of visual function. However, it is too early to make any conclusion until the reproducibility of the results is confirmed in prospective studies involving more patients.

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