ORIGINAL CONTRIBUTION

Microcystic Inner Nuclear Layer Abnormalities and Neuromyelitis Optica

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Importance: Microcystic abnormalities involving the inner nuclear layer of the retina occurs in a subset of patients with multiple sclerosis, most commonly in eyes previously affected by symptomatic optic neuritis. Acute optic neuritis is a cardinal manifestation of neuromyelitis optica (NMO). To our knowledge, microcystic inner nuclear layer abnormalities have not been investigated in NMO.

Objective: To establish whether microcystic inner nuclear layer abnormalities occur in NMO.

Design: Observational, retrospective study.

Setting: University of California at San Francisco Multiple Sclerosis Center (academic specialty clinic).

Patients: Twenty-five consecutive patients with NMO based on 2006 diagnostic criteria or with NMO spectrum disease (defined by seropositivity for anti–aquaporin 4 IgG in the context of a single episode of transverse myelitis or optic neuritis).

Exposure: Spectral-domain optical coherence tomography.

Main Outcomes and Measures: Identification of microcystic inner nuclear layer pathology on spectral-domain optical coherence tomography. Multivariable linear regression was used to examine associations between microcystic changes and measures of retinal structure and function. The hypothesis was generated prior to the data being reviewed and analyzed.

Results: Microcystic changes were identified in 5 of 25 patients with NMO (20%) and 7 of 48 total eyes, including 7 of 29 eyes (24%) previously affected by optic neuritis. Microcystic changes occurred exclusively in eyes with a history of acute symptomatic optic neuritis (100% of eyes with microcystic changes had experienced prior optic neuritis compared with 71% of NMO eyes without microcystic abnormalities). There were no significant differences between patients with NMO with and without microcystic changes in terms of age, sex, and aquaporin 4–IgG antibody status. The mean age in this cohort was 44 years (range, 13-81 years); 84% were women; 80% were aquaporin 4–IgG seropositive; and the median Expanded Disability Status Scale score was 4.0 (interquartile range, 3.0-6.5).

Conclusions and Relevance: Microcystic inner nuclear layer pathology occurs in a proportion of patients with NMO in eyes previously affected by acute optic neuritis. Additional research is needed to understand the cause of this retinal pathology and determine whether it contributes to persistent visual disability in patients with NMO following optic neuritis.

JAMA Neurol. 2013;70(5):629-633. Published online March 25, 2013. doi:10.1001/jamaneurol.2013.1832

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NEUROMYELITIS OPTICA (NMO) is an inflammatory disease of the central nervous system characterized by injury to the optic nerve, spinal cord, brainstem, and brain parenchyma.[1,2] Once thought to be an aggressive variant of multiple sclerosis (MS), NMO is now known to have a distinctive pathophysiology characterized, in part, by an antibody-mediated attack against central nervous system aquaporin 4,[3-5] a water channel expressed by astrocytes.[6-8] Serum IgG-1 antibodies to aquaporin 4 are detectable in about 80% of patients with NMO and are highly specific for the diagnosis.[3,9,10]

Optic neuritis is a defining feature of NMO and typically leads to optic nerve demyelination,[11] profound retinal nerve fiber layer (RNFL) axonal loss,[12-16] retinal ganglion cell loss,[17] and severe visual disability.[18-20] Optic neuropathy in NMO is also sometimes associated with peripapillary retinal vascular abnormalities, including focal arteriolar narrowing and attenuation of the peripapillary vascular tree.[15]

Microcystic macular edema, a novel retinal phenotype characterized by honeycombed, microcystic abnormalities of the inner nuclear layer on optical coherence tomography (OCT), was recently identified and confirmed to occur in about

5% of patients with MS.[21,22] Microcystic inner nuclear layer abnormalities have also been observed histologically following optic nerve transection[23-25] and as rare findings in other types of human optic nerve injury,[26] but this finding has not been consistently replicated in other model systems of optic nerve injury.[27,28]

In this study, we sought to establish whether microcystic inner nuclear layer pathology occurs in NMO.

METHODS

PARTICIPANTS

We retrospectively identified consecutive patients with NMO based on 2006 diagnostic criteria[29] or with NMO spectrum disease (defined by seropositivity for anti–aquaporin 4 IgG in the context of a single episode of transverse myelitis or optic neuritis) who had received spectral-domain (SD)–OCT imaging at our referral center as part of routine clinical care between 2008 and 2012. Exclusion criteria included diabetes mellitus, glaucoma, uveitis, eye trauma, or other retinal disease. A history of acute optic neuritis was defined clinically and was obtained by participant report and medical record review. The Expanded Disability Status Scale (EDSS) score,[30] a measure of functional disability typically used in MS but also potentially informative in NMO, was assigned by the treating neurologist. Aquaporin 4 antibody testing was obtained from one of several commercial laboratories.

ETHICAL CONSIDERATIONS

All patients provided written informed consent. The University of California at San Francisco Committee on Human Research approved the study protocol.

OCT

Spectral-domain OCT imaging was obtained using the Heidelberg Spectralis OCT system. For evaluation of the macula, we used raster scans of the macula (20° × 15°) consisting of 19 line scans in a rectangular section. A 360° peripapillary RNFL B-scan was obtained at a distance of 3.4 mm from the center of the papilla and mean RNFL thickness was calculated using Heidelberg software.[31] Laboratory-quality control measures included review of all source images to ensure adequate signal to noise, a good fit, and the absence of other significant retinal or optic nerve pathology. Our laboratory target for macular scans was an automatic real-time (the number of B-scan images used to construct the final A-scan image) of 48 and a quality score (a measure of signal to noise) of 20. A trained technician obtained all OCTs. Microcystic inner nuclear layer abnormalities were defined as cystic, honeycombed, lacunar areas of hyporeflectivity with clear boundaries on SD-OCT macular raster scan images, excluding speckling artifact.[21]

VISUAL TESTING

High-contrast visual acuity was measured using a computerized Early Treatment Diabetic Retinopathy Study chart (ProVideo) under standard lighting conditions in the same examination room using a standardized laboratory protocol. Low-contrast visual acuity was obtained using a computerized chart (ProVideo) at 20/200, assigning a score between 0 and 100 based on the lowest contrast at which participants could read the letters (100 points for reading at 1.2% contrast, 5 points for the ability to read at 100% contrast, and 0 points for the inability to read at 20/200). Color vision was tested using Hardy-Rand-Rittler color plates.[32]

STATISTICAL ANALYSIS

Multivariable linear regression was used to examine associations of microcystic inner nuclear layer pathology with foveal thickness, macular volume, RNFL thickness, visual acuity, and EDSS, with models adjusting for age and sex and, when appropriate, history of optic neuritis. Within-patient intereye correlations were accounted for using the robust clustered sandwich estimator. Differences in baseline variables between groups were analyzed using the *t* test for age, the χ^2 test for sex, the Fisher exact test for optic neuritis, and the Wilcoxon rank-sum test for EDSS and time from first and most recent acute optic neuritis. Stata version 12.0 (StataCorp) was used for all analyses.

RESULTS

We identified 23 patients with NMO and 2 patients with NMO spectrum disorder (both with optic neuritis and positive anti–aquaporin 4 IgG) who had received SD-OCT imaging in our laboratory as part of routine clinical care between 2008 and 2012. The mean (SD) age of this cohort was 44.2 (18.5) years (range, 13-81 years); 84% were women; 15 (60%) were white (of whom 2 were of Hispanic ethnicity), 7 (28%) were Asian, and 3 (12%) were black; 80% were aquaporin 4–IgG seropositive; and the median EDSS score was 4.0 (interquartile range, 3.0-6.5). Two eyes were excluded from analysis owing to difficulty obtaining interpretable scans in the context of severe visual loss.

Microcystic inner nuclear layer pathology was identified on SD-OCT in 5 patients (20%) and in 7 of 48 eyes (15%), including 7 of 29 eyes (24%) previously affected by optic neuritis (**Table**; **Figure**; eFigure, http://www.jamaneuro.com). When compared with patients with MS who underwent this identical diagnostic analysis at our institution,[21] microcystic changes were more common in patients with NMO (20%, 5 of 25) in our data set than in those with MS (5%, 15 of 318) ($P = .01$; Fisher exact test). Microcystic abnormalities occurred exclusively in eyes previously affected by acute optic neuritis (100% of eyes with microcystic changes had prior optic neuritis compared with 71% of NMO eyes without microcystic changes; $P = .17$). The median time from the first optic neuritis episode in the group with microcystic changes was 6.4 years (interquartile range, 5.6-10.2 years) compared with 4.5 years (interquartile range, 0.4-8.6 years) in NMO optic neuritis eyes without microcystic changes ($P = .16$). There were no appreciable differences in age, sex, aquaporin 4 antibody seropositivity, or EDSS score between patients with and without microcystic changes.

High-contrast and low-contrast vision and color vision trended lower in eyes with microcystic changes, but this difference did not reach statistical significance. The total RNFL was thinner in eyes with microcystic changes compared with all NMO eyes without microcystic changes (18.9 μm less; 95% CI, −3.0 to −34.8; $P = .02$; adjustment for age and sex did not influence the magnitude of the effect or the statistical significance). The total RNFL was 6.6 μm lower in eyes with microcystic changes com-

Table. Demographics, Visual Function, and Retinal OCT Findings

	Neuromyelitis Optica, Median (IQR)		
	Without Microcystic Inner Nuclear Changes	With Microcystic Inner Nuclear Changes	*P* Value
Age, mean (SD), y	45.6 (19)	38.6 (17)	.46
Female, %	85	80	>.99
Expanded Disability Status Scale score	4 (3.0 to 6.5)	6 (3.0 to 6.5)	.81
Eyes with prior acute optic neuritis, No. (%)	29 (71)	7 (100)	.17
Optic neuritis episodes per affected eye	1 (1 to 2)	2 (1 to 3)	.49
Range	1-6	1-4	
Time since first ever acute optic neuritis, y	4.5 (0.4 to 8.6)	6.4 (5.6 to 10.2)	.16
Time since most recent acute optic neuritis, y	1.5 (0.2 to 4.0)	5.6 (0.4 to 6.1)	.34
High-contrast visual acuity, LogMAR units[a]			
All eyes	0.1 (−0.1 to 1.6)	1.6 (0 to 3.0)	.08
Eyes with prior optic neuritis	0.5 (0 to 3.0)	1.6 (0 to 3.0)	.36
Low-contrast acuity	56 (0 to 86)	0 (0 to 39)	.22
Color vision (using HRR plates, calculated as best out of 19)	7 (0 to 16)	0 (0 to 17)	.73
Total retinal nerve fiber layer thickness, mean (SD), μm			
All eyes	68.0 (28.2)	49.1 (16.2)	.02
Eyes with prior optic neuritis	55.7 (24.2)	49.1 (16.2)	.41
Total macular volume, mean (SD), mm^3			
All eyes	2.83 (0.20)	2.85 (0.14)	.75
Eyes with prior optic neuritis	2.76 (0.19)	2.85 (0.14)	.18
Foveal thickness, mean (SD), μm			
All eyes	255.3 (20.2)	264.0 (15.5)	.19
Eyes with prior optic neuritis	254.7 (21.8)	264.0 (15.5)	.19

Abbreviations: HRR, Hardy-Rand-Rittler; IQR, interquartile range; OCT, optical coherence tomography.

[a]The LogMAR scale is commonly used for statistical analysis of visual acuity and is calculated as the logarithm (base 10) of the decimal value on the Snellen scale. For example, 20/20 acuity is 0 on the LogMAR scale, whereas 20/200 is 1.0 on the LogMAR scale and 20/10 is −0.30.[33]

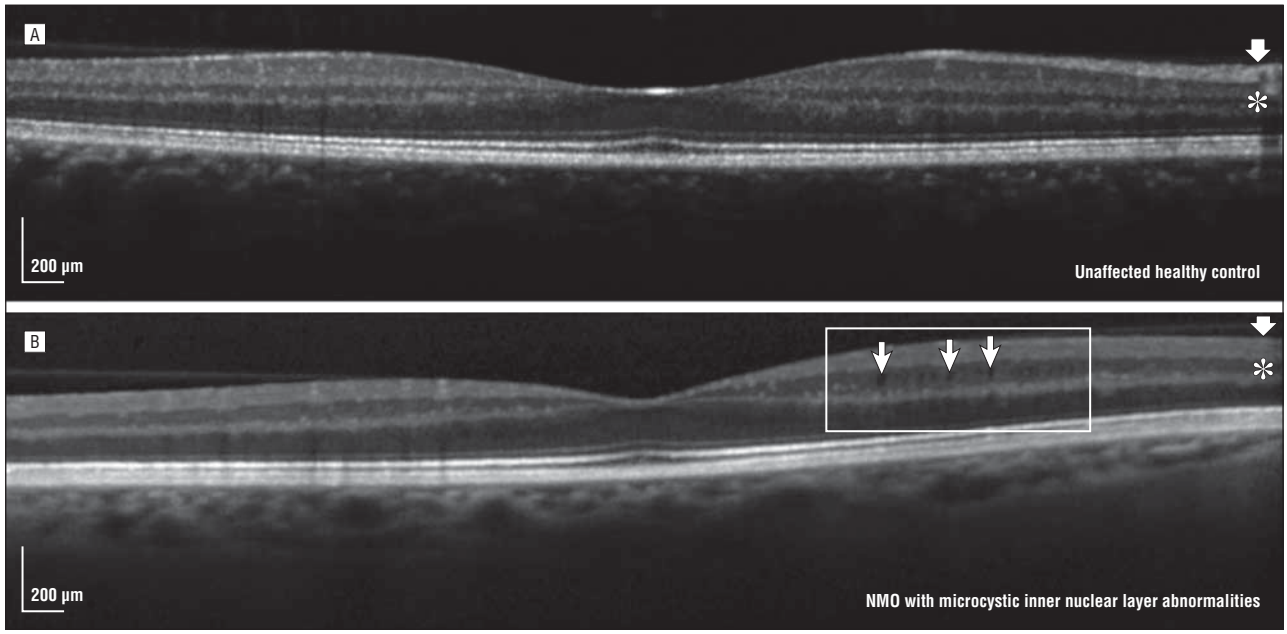

Figure. For comparison, scans of a healthy patient vs an affected patient. A, Representative macular scan of an unaffected healthy woman. B, Microcystic macular abnormalities of the inner nuclear layer on spectral-domain optical coherence tomography in a patient with neuromyelitis optica (NMO) in an eye with prior optic neuritis. The rectangular box highlights the area of microcystic abnormalities, and the thin arrows point to exemplary cysts. The asterisks denote the inner nuclear layer. Note that the retinal nerve fiber layer (arrowheads) is also thinner in the patient with NMO.

pared with NMO eyes with prior optic neuritis without microcystic changes (95% CI, 9.7 to −23.0; *P* = .41). Total macular volume trended 0.09 mm^3 higher (95% CI, 0.22 to −0.05; *P* = .18) in the group with microcystic changes compared with NMO optic neuritis eyes without microcystic changes, but the confidence intervals were too broad to exclude the possibility of no association. Foveal thickness also trended higher in eyes with microcystic changes (8.7 μm higher compared with eyes without microcystic changes; 95% CI, −4.4 to 21.7; *P* = .19; and 9.3 μm higher than optic neuritis eyes without microcystic changes; 95% CI, −4.9 to 23.4; *P* = .19).

COMMENT

The main finding of this study was that microcystic abnormalities of the inner nuclear layer were detectable on SD-OCT in 20% of patients with NMO and 24% of NMO optic neuritis eyes. Furthermore, this microcystic inner nuclear layer pathology in NMO was observed exclusively in eyes previously affected by optic neuritis.

Microcystic inner nuclear layer abnormalities on OCT were recently observed in about 5% of patients with MS and were associated with greater MS disease severity and decreased visual acuity.[21,22] While the sample size of the NMO group with microcystic abnormalities was small, which could have influenced the statistical analysis, the results from this study suggest that the prevalence of microcystic inner nuclear layer pathology on SD-OCT appears to be substantially higher in NMO. This may relate to differences in pathophysiology between the 2 conditions, as optic neuritis in NMO tends to be more aggressive and more destructive, as well as leads to greater visual disability than it does in MS.[13,14,18,20] As microcystic inner nuclear layer abnormalities were observed exclusively in NMO eyes previously affected by optic neuritis, these results support the idea that optic nerve injury is necessary (but not necessarily sufficient) to cause microcystic inner nuclear layer pathology.

The cause of microcystic inner nuclear layer pathology in MS and NMO is unknown, but it may relate to transsynaptic degeneration following optic nerve injury,[23,24] local disruptions in the blood-retinal barrier, focal retinal inflammation, and/or microglial activation in response to neuronal and axonal loss and/or injury. Some have proposed calling this OCT phenotype microcystic macular degeneration of optic neuropathy.[34] Interestingly, in the context of NMO, aquaporin 4 water channels are abundantly expressed by Müller cells, retinal glia located within and around the inner nuclear layer that are involved in blood-retinal barrier functioning[35] and osmotic regulation.[8] Aquaporin 4 channels also appear to serve a neuroprotective function following acute ischemic injury in mice.[36] More research is needed to determine whether Müller cells are ever an antigenic target in NMO or whether Müller cells are involved in microcystic pathology in MS and NMO.

This study has some important limitations. First, the sample size was relatively small, which limited statistical power, especially for determining associations with other clinical variables (including visual function and overall disease disability). Second, comprehensive ophthalmological examinations were not routinely performed. Third, the profound degree of visual disability in NMO may have made it more difficult to discern potential contributions of this retinal pathology to persistent visual dysfunction. And finally, the possible effects of disease-modifying therapy on microcystic changes were not assessed. As patients with NMO are typically, but not always,[37-39] treated with different disease-modifying therapies than patients with MS, we cannot exclude a contribution of therapy to the observed difference in microcystic changes between MS and NMO. A relative strength of this study is that the demographics of the patients with NMO studied were similar to other published cohorts.[40-42]

In conclusion, microcystic abnormalities of the inner nuclear layer on SD-OCT are relatively common in NMO eyes previously affected by optic neuritis. Further research is needed to understand the cause of this retinal pathology and elucidate whether it contributes to persistent visual disability in patients with NMO following optic neuritis.

Accepted for Publication: November 16, 2012.
Published Online: March 25, 2013. doi:10.1001/jamaneurol.2013.1832
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Author Contributions: *Study concept and design:* Gelfand, Cree, Nolan, and Green. *Acquisition of data:* Gelfand, Cree, Nolan, and Green. *Analysis and interpretation of data:* Gelfand, Cree, Arnow, and Green. *Drafting of the manuscript:* Gelfand. *Critical revision of the manuscript for important intellectual content:* Cree, Nolan, Arnow, and Green. *Statistical analysis:* Gelfand. *Obtained funding:* Green. *Administrative, technical, and material support:* Cree, Nolan, and Green. *Study supervision:* Cree and Green.
Conflict of Interest Disclosures: Dr Gelfand has received honoraria from the National Multiple Sclerosis Society for patient education. Dr Cree has received personal compensation for consulting with Biogen-Idec, EMD Serono, Novartis, Sanofi-Aventis, and Teva Neurosciences. Dr Green has provided consulting services for Prana Pharmaceuticals, Novartis, Biogen, Roche, and Acorda Pharmaceuticals. Dr Green has served on an end point adjudication committee for a Biogen-sponsored trial and provided expert legal advice for Mylan Pharmaceuticals.
Funding/Support: This study was supported by funding from the American Academy of Neurology Clinical Research Training Fellowship (Dr Gelfand) and grant KL2 RR 024130 from the National Institutes of Health (Dr Green).
Online-Only Material: The eFigure is available at http://www.jamaneuro.com.

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