

Usefulness of optical coherence tomography to distinguish optic neuritis associated with AQP4 or MOG in neuromyelitis optica spectrum disorders

Elena H. Martinez-Lapiscina*, Maria Sepulveda*, Ruben Torres-Torres, Salut Alba-Arbalat, Sara Llufríu, Yolanda Blanco, Ana M. Guerrero-Zamora, Nuria Sola-Valls, Santiago Ortiz-Perez, Pablo Villoslada, Bernardo Sanchez-Dalmau and Albert Saiz

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory central nervous system disease that preferentially affects the optic nerve and spinal cord [Wingerchuk *et al.* 2015]. Up to 70% of patients with NMOSD have antibodies to aquaporin-4 (AQP4-IgG). AQP4 is expressed in astrocytes of the optic nerve and Müller cells in the eye. A subgroup of AQP4-IgG-seronegative patients has antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG), and optic neuritis (ON) relapses are also frequent in these patients [Höftberger *et al.* 2015].

We hypothesize that retinal injury may be additionally driven by Müller cells dysfunction in patients with AQP4-IgG. This condition, in contrast with those patients who harbour MOG-IgG, may induce differential changes in the outer retinal layers. In this brief series of cases, we aim to investigate if optical coherence tomography (OCT) may distinguish ON associated with AQP4-IgG or MOG-IgG in NMOSD.

Methods

We included 15 ON eyes from five patients diagnosed with NMOSD and AQP4-IgG and four patients who fulfilled the new diagnostic criteria for NMOSD without AQP4-IgG [Wingerchuk *et al.* 2015] and who had MOG-IgG. AQP4-IgG and MOG-IgG were tested by cell-based assays as reported [Höftberger *et al.* 2015]. The presence of prior ON was assessed following international guidelines [Petzold *et al.* 2014]. Patients suffered bilateral ON, except for one patient in each group who only developed a unilateral ON. In addition,

one ON eye of a patient with MOG-IgG was excluded due to the low quality of the OCT scan. Thus, we included 15 NMOSD-ON eyes (nine ON eyes with AQP4-IgG and six ON eyes with MOG-IgG). As a group of comparison, we selected 15 ON eyes of 15 MS patients with at least one prior ON episode (MS-ON eyes). We retrieved the MS patients whose age better matched NMOSD patients' age from our general data set of MS patients (nine matched with AQP4-IgG-seropositive patients and six with MOG-IgG-seropositive patients). The period of time from the last ON episode to the visual examination was at least six months for all cases. Patients gave consent to participate, and the institutional review board of the Hospital Clinic, University of Barcelona, Spain, approved the study.

We evaluated visual acuity, colour vision and visual fields as previously described [Martínez-Lapiscina *et al.* 2014]. The retinal scans were performed using a Spectralis® SD-OCT device (Spectralis® Heidelberg Engineering, Heyex 5.30) by a trained technician under standard ambient light conditions and without pupillary dilatation, using eye-tracking modality. Correction for spherical errors was adjusted prior to each measurement. The peripapillary retinal nerve fibre layer (pRNFL) thickness (μm) was measured using a ring scan of 12 degrees of diameter, automatically centred on the optic nerve head (100 ART; 1536 A scans per B scan). The macular scan protocol was a 20×20 degree raster scan (horizontal orientation) centred on the fovea, including 25 high-resolution B scans (ART ≥ 9 ; 512 A scans per B scan). A single masked grader performed intraretinal layer segmentation using the same standard 6.0c version of the

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Correspondence to:

Elena H. Martínez-

Lapiscina, MD PhD

Maria Sepulveda

Salut Alba-Arbalat

Sara Llufríu

Yolanda Blanco

Ana M. Guerrero-Zamora

Nuria Sola-Valls

Albert Saiz

Center of

Neuroimmunology and

Service of Neurology,

August Pi Sunyer

Institute of Biomedical

Research, Hospital Clinic

of Barcelona, University

of Barcelona, Barcelona,

Spain.

hernandez@clinic.ub.es

Ruben Torres-Torres

Santiago Ortiz-Perez

Bernardo Sanchez-

Dalmau

Service of Ophthalmology,

Institut d'Investigacions

Biomèdiques August Pi

Sunyer (IDIBAPS), Hospital

Clinic of Barcelona,

University of Barcelona,

Barcelona, Spain

Pablo Villoslada

Center of

Neuroimmunology and

Service of Neurology,

August Pi Sunyer Institute

of Biomedical Research,

Hospital Clinic of Barcelona,

University of Barcelona,

Barcelona, Spain

Multiple Sclerosis Center,

Department of Neurology,

University of California,

San Francisco (UCSF), San

Francisco, CA, USA

*These authors

contributed equally to this

work.

Table 1. Comparison of visual outcomes between NMOSD-ON eyes with AQP4-IgG and MOG-IgG and age-matched MS-ON eyes.

	AQP4 ⁺ NMOSD-ON eyes [1]	MS-ON eyes [2]	<i>p</i> value [1-2]	MOG ⁺ NMOSD-ON eyes [3]	MS-ON eyes [4]	<i>p</i> value [3-4]
Sex n [%] (female)	6 [66%]	7 [77%]	0.910	3 [50%]	2 [33%]	0.558
Age (years)	34.9 [19.4-43.8]	32.6 [27.6-36.7]	0.965	54.4 [53.4-58.1]	49.7 [42.2-61.5]	0.240
Number of ON	2 [1-3.5]	2 [1-2]	0.352	1.5 [1-4]	2 [1-2.25]	0.932
Time since last ON (months)	86.4 [15.2-107.3]	28.1 [14.1-100.2]	0.436	99.0 [21.4-185.8]	139.1 [69.1-169.6]	0.485
HCVA (#0-70 letters)	45 [28-64]	58 [50-60]	0.565	47 [40-56]	55 [41-56]	0.310
2.5% LCVA (#0-70 letters)	0 [0-20]	21 [3-30]	0.159	13 [0-30]	27 [0-30]	0.662
1.25% LCVA (#0-70 letters)	0 [0-0]	4 [0-20]	0.031	0 [0-6]	10 [0-18]	0.247
HRR (#0-36 symbols)	21 [6-36]	36 [29-36]	0.052	35 [17-36]	31 [12-35]	0.329
Visual field (MD) (dB)	-5.9 [-12.5 to -0.5]	-4.3 [-6.5 to -2.2]	0.831	-2.7 [-4.7 to -1.9]	-2.5 [-6.6 to -1.7]	0.841
pRNFL thickness (µm)	50 [40-77]	80 [72-90]	0.038	68 [48-78]	74 [65-78]	0.310
mGCC thickness (µm)	67 [62-100]	91 [78-99]	0.112	82 [62-93]	83 [65-92]	0.872
INL thickness (µm)	43 [42-46]	39 [37-42]	0.021	40 [37-41]	40 [40-42]	0.565
OPL thickness (µm)	30 [29-33]	35 [32-38]	0.008	30 [28-37]	32 [30-36]	0.626
ONL thickness (µm)	80 [78-81]	71 [65-75]	0.021	75 [68-80]	76 [71-81]	0.872
PR thickness (µm)	80 [78-81]	82 [80-84]	0.190	81 [77-83]	82 [80-86]	0.416

Data represents median [P25-P75] unless otherwise indicated. Chi-squared Pearson test for categorical variables and Mann-Whitney *U* test for quantitative variables.

AQP4⁺: antibodies against Aquaporin 4; HCVA: high contrast visual acuity; HRR: Hardy, Rand and Rittler pseudoisochromatic plates; INL: macular inner nuclear layer; LCVA: low contrast visual acuity; MD: mean deviation; mGCC: macular ganglion cell complex; MOG⁺: antibodies against myelin oligodendrocyte glycoprotein; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; OCT: optical coherence tomography; ON: optic neuritis; ONL: macular outer nuclear layer; OPL: macular outer plexiform layer; PR: photoreceptors including retinal pigment epithelium and Bruch membrane; pRNFL: peripapillary retinal nerve fibre layer.

Spectralis segmentation algorithm in a semi-automated fashion, with manual correction of obvious errors to quantify macular ganglion cell complex (mGCC) including the retinal nerve fibre; ganglion cell and inner plexiform layers; inner nuclear layer (INL); outer plexiform layer (OPL); outer nuclear layer (ONL) and photoreceptors (PR) including retinal pigment epithelium retinal and Bruch membrane.

We separately included both NMOSD-ON eyes of each patient, rather than using the mean of both eyes, because even though some studies showed a mild retinal injury in non-ON eyes in NMOSD [Monteiro *et al.* 2012], a recent review suggested that the visual impairment in NMOSD is basically attributable to the ON episodes [Bennett *et al.* 2015]. Using the Mann-Whitney *U* test, we compared visual outcomes in the two groups and thereafter, we repeated analyses stratifying by antibody status. Two-tailed *p* values

<0.05 were considered significant. Analyses were performed with the statistical package IBM-SPSS 20.0 software.

Results

We did not find significant differences in sex, age, number of ON episodes, and median time between last ON and visual examination in NMOSD-ON and MS-ON eyes in our study. NMOSD-ON eyes displayed poorer visual outcomes compared with MS-ON, although differences were only significant for low-contrast visual acuity. NMOSD-ON eyes displayed thinner pRNFL compared with MS-ON eyes. NMOSD-ON eyes showed thinner OPL and thicker ONL compared with MS-ON eyes (data not shown). We did not find microcystic macular oedema in any of the ON eyes.

Table 1 shows visual outcomes for NMOSD-ON eyes. Patients with MOG-IgG were older than

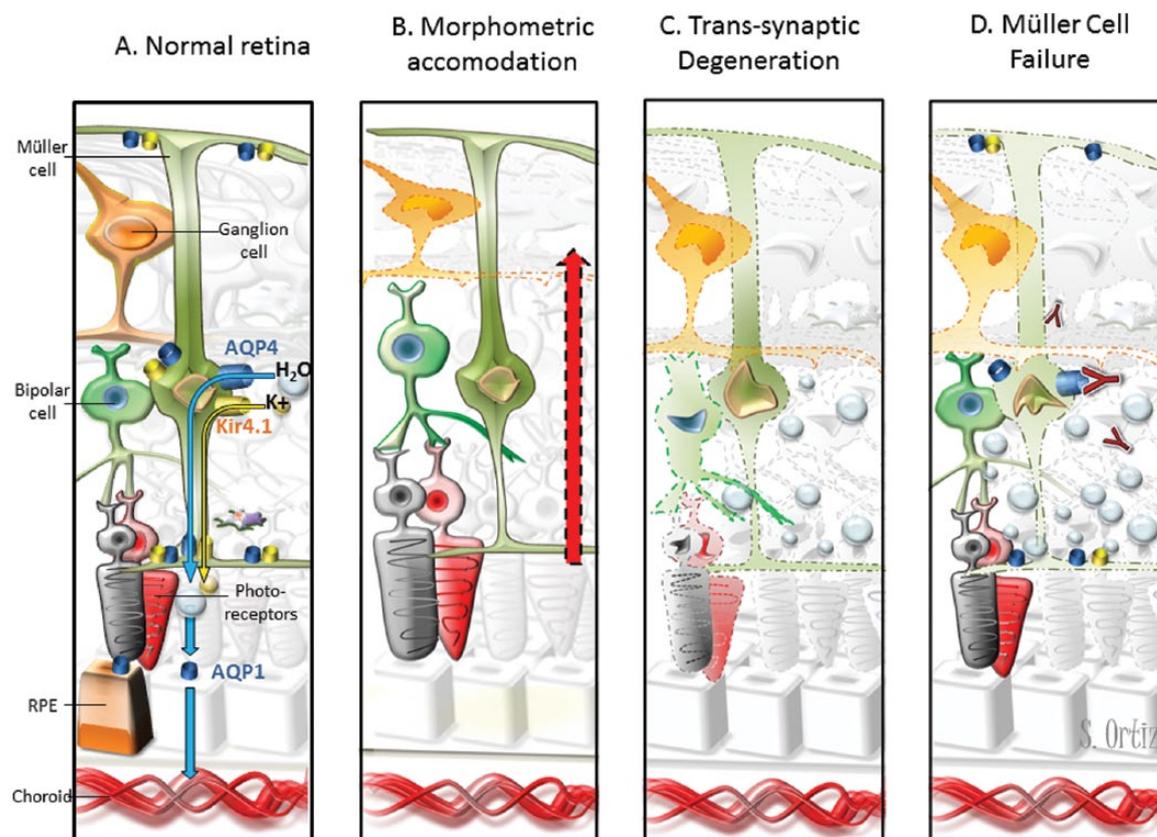


Figure 1. Pathogenic models of retinal damage in NMOSD-ON eyes.

(A) Water transportation through the retina. Extracellular fluid accumulates in the neural retina and subretinal space. Müller cells and RPE cells promote fluid clearance towards the vessels using aquaporins receptors. Müller cells express AQP4, and RPE cells express AQP1. Moreover, water transportation is coupled to the transport of potassium through Kir4.1 channels. Müller cells display AQP4 and Kir4.1 surrounding the vessels of INL and at both limiting membranes. (B) The hypothesis of morphometric accommodation. Müller cells may promote thickening of other layers as compensatory effect to mGCC thinning after AON. We would expect proportional or greater thickening in adjacent layers (INL/OPL) and we found thickening of INL and ONL but OPL thinning. (C) The hypothesis of trans-synaptic degeneration. Retrograde degeneration of ganglion cells may induce trans-synaptic degeneration that finally lead to neuronal loss in the retina. Neuronal loss would translate in layer thinning instead of thickening. However, trans-synaptic degeneration may promote Müller cell dysfunction with fluid accumulation leading to retinal thickening that mask neuronal loss. (D) The hypothesis of Müller cell dysfunction. Inflammation in the acute phase of optic neuritis may induce Kir4.1 down regulation leading to water accumulation and transient thickening of outer layers [Gabilondo *et al.* 2015]. In patients with AQP4-antibodies, the immune-mediated damage may promote Müller cells loss. This would likely produce water accumulation in the neural retina but not in the subretinal space because RPE cells express AQP1. In our study, NMOSD-ON eyes patients with AQP4-IgG displayed INL and ONL thickening but not RPE thickening. AQP, aquaporin; INL, inner nuclear layer; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; RPE, retinal pigment epithelium; AON, acute optic neuritis; mGCC, macular ganglion cell complex; ONL, outer nuclear layer; OPL, outer plexiform layer.

patients with anti-AQP4 antibodies. Therefore, to avoid the influence of the age in the visual outcomes, both groups of NMOSD patients, according to the antibody serostatus, were age-matched with MS-ON eyes. Compared with MS-ON eyes, only ON eyes of patients with AQP4-IgG displayed thinner pRNFL. Additionally, they showed thicker INL, thinner OPL and thicker ONL. However, we did not find differences in OCT thicknesses between ON eyes of patients with MOG-IgG and MS-ON eyes.

Discussion

The OCT findings of our comparative study highlight important observations. First, serostatus stratification in NMOSD is important, because a different type of retinal cell damage may occur in patients with NMOSD who share a similar clinical phenotype but have a different antibody profile. Second, ON eyes of patients with AQP4-IgG displayed a distinguished outer retinal OCT macular phenotype (OPL thinning and ONL thickening). Third, OCT results of

ON eyes of patients with MOG-IgG were similar to those found with MS-ON eyes.

Previous studies found that NMOSD-ON eyes typically displayed thinner pRNFL and mGCC as compared with MS-ON eyes [Bennett *et al.* 2015]. However, the evidence of involvement of other layers was scarce. Previous studies have described INL thickening in patients with NMOSD compared with MS [Fernandes *et al.* 2013] and OPL thinning with ONL thickening compared with isolated ON eyes and MS eyes [Park *et al.* 2014]. However, none of these studies analyzed these findings according to the antibody serostatus in patients with NMOSD.

The novelty of this brief study is that we addressed differences in NMOSD according to serostatus and the results suggest that even the clinical profile is similar, pathophysiological mechanisms underlying neuroaxonal damage are different in these two entities. In Figure 1, we discuss several biological processes that may explain the changes in outer retinal layers in ON eyes when associated with AQP4-IgG. INL thickening has been described in ON eyes of patients with MS. Some authors have proposed that INL thickening and microcystic macular oedema may be a continuum and represents trans-synaptic degeneration in the retina [Saidha *et al.* 2012]. However, we suggest that antibody-mediated damage of Müller cells is likely a key and specific contributor to the outer retinal damage observed in patients with AQP4-IgG. Moreover, the absence of differences between patients with ON associated with MOG-IgG or MS suggests that the physiopathological mechanism involved in both disorders may be similar. In fact, a MS-type pattern II was found in a recent histopathological study of one patient with MOG-IgG [Spadaro *et al.* 2015]. Altogether, this suggests that the neuroaxonal injury may be driven by different mechanisms: astrocytopathy for AQP4+ NMOSD and oligodendropathy for MOG+ NMOSD and MS patients.

In conclusion, OCT seems to be a useful tool to evaluate the underlying retinal damage related to the different serostatus in patients with NMOSD; however, larger and longitudinal studies are needed to confirm the results of the current exploratory study.

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Conflict of interest statement

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