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Original Research Paper

Early retinal atrophy predicts long-term visual impairment after acute optic neuritis

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Abstract

Background: Visual recovery after optic neuritis (ON) used to be defined as good, although patients frequently complain of poor vision.

Methods: We carried out a prospective study on 38 consecutive patients with acute ON followed monthly for 6 months and evaluated high- and low-contrast visual acuity (HCVA and LCVA, respectively), quality of vision (National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)), visual fields, and retinal thickness by spectral domain optical coherence tomography (OCT).

Results: We found significant impaired LCVA and color vision in ON eyes 6 months after acute ON, which impact on quality of life. LCVA and color vision were correlated with the thicknesses of the ganglion cell and inner plexiform layer (GCIPL; 2.5% LCVA $r=0.65$ and $p=0.0001$; color vision $r=0.75$ and $p<0.0001$) and that of the peripapillary retinal nerve fiber layer (pRNFL; LCVA $r=0.43$ and $p=0.0098$; color vision $r=0.62$ and $p<0.0001$). Linear regression models that included the change in the GCIPL and pRNFL thicknesses from baseline to month 1 after onset explained 47% of the change in 2.5% LCVA and 67% of the change of color vision acuity. When adjusting for the value of visual acuity at baseline, predictors of the change in vision from baseline to month 6 achieved similar performance for all three types of vision (HCVA, LCVA, and color vision).

Conclusion: Monitoring retinal atrophy by OCT within the first month after ON onset allows individuals at a high risk of residual visual impairment to be identified.

Keywords: Acute optic neuritis, multiple sclerosis, quality of vision, visual acuity, visual field, color vision, perimetry, optical coherence tomography

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Introduction

Optic neuritis (ON) occurs commonly as the onset of multiple sclerosis (MS) or during the course of the disease, although it may also be an isolated condition (idiopathic), significantly deteriorating the quality of vision in young people.[1–3] A good recovery from ON is usually defined when measuring visual impairment using high-contrast visual acuity (HCVA) charts, leading to the misconception that ON is a benign condition.[4,5] However, when more sensitive measurements are used, such as low-contrast visual acuity (LCVA), color vision, motion perception, and detailed quality of vision scales, patients who have suffered ON often display significant impairments that limit their daily life.[4–8] For example, it was recently shown that patients with a history of acute ON that was associated with recovery to 20/40 or better in the HCVA had significantly worse quality of vision (assessed with the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) and 10-Item Neuro-Ophthalmic Supplement) than healthy volunteers.[5]

In order to improve patient management and develop more effective therapies for ON, it is critical to have biomarkers or imaging markers that identify individuals at high risk of suffering visual impairment in the long term. Although the severity of visual loss at presentation or some features of optic nerve magnetic

resonance imaging (MRI) are associated with a worse outcome, the accuracy of these parameters is limited to use in clinical practice or clinical trials.[9–12] Hence, we set out to evaluate visual function after acute ON in a prospective cohort study and to identify predictors of residual visual impairment that may be readily detected and useful in clinical practice or in clinical trials to improve patient management.

Methods

Study population

From January 2011 to July 2014, we prospectively recruited consecutive patients with acute ON attending the Department of Ophthalmology and the Department of Neurology at the Hospital Clinic of the University of Barcelona, as described previously.[13] We included subjects between 18 and 55 years of age with demyelinating ON, including idiopathic ON, clinically isolated syndrome, or previously diagnosed MS,[14] yet we excluded subjects with neuromyelitis optica spectrum disorders or chronic relapsing inflammatory optic neuropathy. Time from clinical onset to inclusion in the study was ⩽2 weeks. Patients underwent extensive neurological and ophthalmological examinations, blood tests (including anti-aquaporin-4 antibody detection), and brain and orbital MRI, in order to confirm the presence of acute ON and to exclude other ophthalmological conditions. Visual evoked potentials (VEPs) were assessed in some patients as part of the diagnostic process but not systematically as a marker of visual impairment. Patients were also excluded if they had severe myopia: >−6.0 dB or axial eye length: >26 mm, severe hypermetropia: >5 dB, cylinder: >3 dB, optic nerve drusen, cataracts, current or previous glaucoma, or other causes of visual loss not attributable to ON.

All patients with ON had their records reviewed for prior episodes of ON.[15,16] As such, cases of prior ON were identified from clinical records and/or based on the peripapillary retinal nerve fiber layer (pRNFL) thickness at baseline ⩽78 µm, a cut-off value that corresponds to the median pRNFL thickness at baseline in eyes with previous ON (ON eyes), as described previously.[17] Patients with a history of ON in the currently affected eye were excluded in this study. Eyes classified as non-ON eyes have neither previous ON nor acute ON. All patients provided their written informed consent prior to enrollment, and the Ethics Committee of the Hospital Clinic of Barcelona approved the study.

Clinical evaluation

We recorded clinical variables from the subjects at the baseline visit such as age, gender, and steroid use, and for patients previously diagnosed with MS, we collected information regarding disease duration, disease sub-type, and the use of disease-modifying therapies (DMTs). All the subjects underwent baseline visual testing and optical coherence tomography (OCT) evaluation prior to initiating steroid treatment. The use of steroid treatment or DMT at any time during follow-up was also recorded. A trained optometrist performed an ophthalmological evaluations (visual acuity) separately on each eye every 2 months from the baseline visit up to month 6 (four assessments in total).

We evaluated the best-corrected HCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, and HCVA letter score was converted to LogMAR units for statistical analysis. LCVA was scored with the Sloan 2.5% and 1.25% contrast charts, and color vision acuity using the Hardy–Rand–Rittler (HRR) plates.[15,18] The scoring of LCVA was based on the number of letters identified correctly (up to 70), and for color vision, we counted the number of HRR symbols correctly identified (up to 36). Before visual acuity and color vision assessment, we evaluated the refraction in all patients even in those patients wearing their own glasses or contact lens. Optical refraction was corrected with the prescription lenses necessary for each refractive problem, positive lenses for hyperopia, negative lenses for myopia, or cylinder lenses for astigmatism. We use the trial lenses frame to use the correct refraction at the same moment.

Visual field (perimetry) analysis was performed only at baseline using the Humphrey perimetry 30-2 full threshold Swedish Interactive Threshold Algorithm (SITA) algorithm (Zeiss Meditec, Dublin, CA, USA), recording the mean standard deviation (MSD). We also performed brain and orbit MRI at baseline and by month 6 using a 3T scanner (Siemens TIM Trio Siemens AG, Medical Solutions, Erlangen, Germany), including the three-dimensional (3D) structural T1-weighted MPRAGE, FLAIR, and T1 spin echo post-gadolinium sequences, as described previously.[17]

Given the lack of normative data for LCVA, inter-eye asymmetry (defined as the LCVA score in the unaffected eye minus that of the affected eye) was established as a difference of at least seven letters at 6 months. Indeed, seven letters in LCVA has been identified as the minimum change to consider a difference as clinically relevant.[18,19] In order to evaluate the

impact of ON on a patient's quality of life (QoL), we analyzed the quality of vision 6 months after ON onset using the NEI-VFQ-25 questionnaire and the 10 neuro-ophthalmological supplement. We used the normative cut-off of abnormal visual quality: global score < 88, 10-neuro-ophthalmological items < 79, and combined score < 85.[20]

Retinal image acquisition and analysis

Retinal scans were performed in a single center by a trained technician (S.A-A.) on a Spectralis® SD-OCT device (Heyex 5.30 Heidelberg Engineering, Heidelberg, Germany) in eye-tracking mode, using standard ambient light conditions (lighting level of 80–100 foot-candles) and without pupillary dilation. Correction for spherical errors was adjusted prior to each measurement. Retinal scans were performed every month from the baseline visit to month 6 (seven evaluations per eye), using the same acquisition protocol on all subjects and were performed in the same week of the other assessments. The pRNFL thickness (μm) was measured using a 12° diameter ring scan automatically centered on the optic nerve head (100 ART; 1536 A scans per B scan). The macular scan protocol involved a 20° × 20° raster scan (horizontal orientation) centered on the fovea, taking 25 horizontal sections separated by 240 μm and with a mean ART ⩾ 9 (512 A scans per B scan).

Retinal layer segmentation was performed automatically using the in-built HRA/Spectralis Viewer Module (v.5.7.5.0) for peripapillary scans and the Viewer Module (beta version v.6.0.0.2) for macular raster scans. Accordingly, we quantified the macular volume (MV) and the thickness of the following layers: (1) pRNFL, (2) macular RNFL (mRNFL), (3) macular ganglion cell and inner plexiform layer (GCIPL), (4) macular inner nuclear layer (INL), (5) macular outer plexiform layer and outer nuclear layer complex (OPL + ONL), and (6) macular external limiting membrane, inner segments, outer segments of photoreceptors, retinal pigment epithelium and Bruch's membrane (photoreceptor layer (PRL)). We analyzed eight of the macular ETDRS sectors, excluding the foveal sector of the ganglion cell layer (GCL) (central 1 mm ring) as this area lacks retinal ganglion cells. A single optometrist (S.A-A.) reviewed all the images from the automated segmentation and performed manual correction of obvious errors. Retinal thickness for each layer was compared between the affected and unaffected eye at baseline and follow-up, except for the pRNFL in which case we used the baseline pRNFL of the fellow eye as reference in order to avoid the confounding effect of optic nerve head swelling. All images were carefully reviewed to ensure the fulfillment of OSCAR-IB and APOSTEL criteria.[21,22]

Statistical analysis

Categorical variables were compared using the Fisher test, and continuous variables were compared with an independent *t* test after confirming their normal distribution (Shapiro test). Analysis was performed using one eye per patient, either the ON eye or the non-ON eye for each subgroup. We used linear regression models to explore the usefulness of retinal layer thickness as a predictive biomarker of vision impairment, including age, sex, disease duration, and the use of DMTs or steroid treatment as covariates. For each clinical scale tested (HCVA, 1.25% and 2.5% LCVA, and color vision), we included first all OCT variables at baseline and 1 month later and the MSD only at baseline. Then, we selected the variables that were significant and included in the final model for each variable (stepwise selection method). The first strategy for identifying predictors of vision impairment to be used in the clinical practice was based on testing easy-to-administer quantitative tests such as OCT and perimetry to predict the clinical outcome, but not the clinical scale at baseline. In the second model, we included the visual scale at baseline in order to evaluate its contribution to the predictor. In order to guaranty that such variable will be kept in the stepwise process, we changed the way of calculating the clinical outcome to the change of HCVA, LCVA, or color vision from baseline to month 6. We have used absolute changes in the calculations of baseline to 1-month changes for OCT variables. In order to account for intra-subject variability, we used paired analysis. All *p* values were two-tailed and they were considered to be significant at $p \leqslant 0.05$. Statistical analyses were performed using SPSS software (SPSS version 20.0: IBM Inc., Chicago, IL, USA).

Results

Visual function and quality of vision after ON

The demographic and clinical characteristics, and the OCT analysis at baseline and 6 months after disease onset, were recorded for the 38 patients with acute ON in our cohort (Table 1). In terms of vision impairment by month 6 after ON, 3 (8.3%) patients had impaired HCVA (LogMAR < 0), 10 (27.7%) had impaired 2.5% LCVA (a seven-letter difference relative to the non-ON eye), 3 (8.3%) had impaired 1.25% LCVA, 7 (19.4%) had impaired color vision (number of figures ⩽ 35), and 11 (31.4%) had impaired visual fields (MSD ⩽ −3 db). The quality of vision was evaluated

Table 1. Demographic and clinical characteristics of patients and the retinal thickness of eyes with acute optic neuritis.

Clinical characteristics		Patients ($n=38$)				
Age (years)		37.12±8.89				
Sex (F/M, % female)		32/6 (84%)				
Previous ON (no. of patients)		5/38				
Unilateral/bilateral ON		37/1				
Previous MS (yes/no)		20/18				
Diagnosis of MS at ON		27/11				
Corticosteroid therapy (i.v.) (yes/no)		27/11				
Vision scales	ON eye baseline	ON eye follow-up	*p* value[a]	Non-ON eye baseline ($n=33$)	Non-ON eye follow-up ($n=33$)	*p* value[b]
HCVA (LogMAR)	0.03±0.22	−0.06±0.08	0.0135	−0.06±0.06	−0.07±0.08	0.1008
LCVA 2.5% (no. of letters)	1.57±5.76	27.11±12.06	<0.00001	29.09±12.21	30.69±10.32	0.0283
LCVA 1.25% (no. of letters)	0.14±0.85	16.14±10.83	<0.00001	16.31±10.48	19.83±10.14	0.0107
Color vision (no. of letters)	23.4±12.3	34.7±3.00	<0.00001	34.91±3.0	35.4±1.9	0.0730
Visual fields (MSD in db)	−15.36±10.57	−2.30±1.51	<0.00001	−2.29±2.06	−2.06±1.08	0.0316
OCT						
pRNFL (μm)	119.57±41.36	93.05±17.35	0.00109	98.92±12.64	98.78±12.35	0.01343
Macular volume (mm^3)	8.73±0.36	8.60±0.38	0.02726	8.69±0.35	8.69±0.34	0.03063
mRNFL (mm^3)	1.02±0.14	0.96±0.17	0.06885	1.01±0.11	1.02±0.10	0.01098
GCIPL (mm^3)	1.95±0.20	1.89±0.25	<0.000001	1.95±0.20	1.96±0.21	0.02404
INL (mm^3)	0.98±0.05	0.97±0.06	0.21815	0.97±0.05	0.96±0.06	0.01128
OPL+ONL (mm^3)	2.65±0.15	2.64±0.14	0.23103	2.62±0.14	2.61±0.14	0.00435
PRL (mm^3)	2.1±0.06	2.18±0.07	0.76681	2.18±0.06	2.17±0.06	0.22630

ON: optic neuritis; MS: multiple sclerosis; HCVA: high-contrast visual acuity; LCVA: low-contrast visual acuity; MSD: mean standard deviation; OCT: optical coherence tomography; pRNFL: peripapillary retinal nerve fiber layer; mRNFL: macular RNFL; GCIPL: ganglion cell and inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer; PRL: photoreceptor layer.
The results are expressed as the mean+standard deviation (except for the number and % for categorical variables). The differences between the baseline and follow-up (month 6) values were assessed with a *t* test or with the Fisher test for categorical variables.
[a]ON eye at baseline vs ON eye at follow-up.
[b]ON eye at follow-up vs non-ON eye at follow-up. Eyes classified as non-ON eyes have no previous ON or acute ON.

with the NEI-VFQ-25 plus 10 neuro-ophthalmological items, finding four patients (21.05%) with pathological global score (<88), seven (36.8%) had an abnormal 10-neuro-ophthalmological item score (<79), and eight patients (42.1%) had a combined pathological score (<85; Table 2).

Changes in the retinal thickness after ON

We found a significant reduction in the pRNFL, mRNFL, GCIPL, and MV of the ON eyes at follow-up relative to the fellow eye (Table 1). Moreover, the reduction in the thickness of the pRNFL, mRNFL, and GCIPL and in the MV from baseline to the first month of follow-up was significantly correlated with the worsening of the HCVA and LCVA, as well as with color vision (Table 3).

Predictors of vision after ON

We were interested in identifying which variables at presentation best predicted the visual outcomes 6 months after ON onset. Such variables should be evident soon after disease onset in order to provide a patient prognosis (risk stratification). As such, we analyzed the clinical and imaging variables at baseline and 1 month later (visual fields were tested only at baseline). We designed multiple linear regression models using retina layer thickness (baseline and the change from baseline to 1 month later) or the MSD of the visual fields (baseline assessment) to predict visual acuity (HCVA, 2.5% LCVA, 1.25% LCVA, and color vision) of ON eyes at follow-up (month 6). First, we tested OCT variables at baseline and the change from baseline to 1 month later, and MSD (baseline), and then we selected the significant variables for the final predictor.

Table 2. Quality of vision after optic neuritis.

	Mean	SD
Global score	89.81	13.19
Supplementary neuro-ophthalmology items	82.61	16.30
Combined score	86.21	13.99
General health	50.00	25.72
General vision	72.00	18.28
Ocular pain	80.00	24.48
Near activities	91.19	15.78
Distance activities	94.52	11.60
Vision specific		
Social functioning	98.93	3.55
Mental health	88.93	16.61
Role difficulties	90.36	19.43
Dependency	95.71	14.63
Driving	84.62	31.77
Color vision	98.57	5.89
Peripheral vision	91.43	17.09

Quality of vision was assessed 6 months after ON onset using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) questionnaire with the 10 neuro-ophthalmological supplement.

In the search of significant OCT variables in the predictors of vision scales 6 month later, we found the best predictors using the change from baseline to month 1 (except for MSD that was collected only at baseline). We performed our analysis in two steps: (1) by including in the modeling the baseline value of the variable to predict at the end of follow-up (HCV, LCVA, or color vision), in order to improve the accuracy of the predictor by reducing the range of the variable and the uncertainty and (2) by controlling the baseline value of such variable in the predictor in order to assess the true contribution of each variable to the predictor (baseline predictors were entered as confounders). For this second approach, we predicted the change from baseline to month 6.

From the first approach, the best prediction of vision by month 6 was achieved for color vision, in which a model including mRNFL and GCIPL thickness explained the 67% of the change in color vision (HRR). The model predicts that a 1-µm decrease in the mRNFL explains 0.4-unit decrease in the HRR by month 6, and a 1-µm decrease in the GCIPL explained a 0.4 unit decrease in the HRR by month 6 (Table 4). Regarding high-contrast vision, a model including the pRNFL decrease from baseline to month 1 and MSD of the visual field value at baseline explained 28% of the change in the HCVA. The ability to predict visual impairment was higher for the 2.5% LCVA, where a model including the thickness of the GCIPL, INL, and mRNFL thickness explained up to 54% of the change in the 2.5% LCVA (a 1-µm decrease in the GCIPL from baseline to month 1 explained a 0.3-unit decrease in the 2.5 LCVA by month 6, a 1-µm increase in the INL from baseline to month 1 explained a 0.2-unit change in the 2.5 LCVA by month 6, and a 1-µm decrease in the mRNFL from baseline to month 1 explained a 0.45-unit decrease in the 2.5 LCVA by month 6. A model including the change in mRNFL thickness on the first month and the MSD of the visual fields at baseline explained 45% of the 1.25% LCVA.

In the second approach (baseline predictors were entered as confounders), we found that the R^2 values were decreased as expected and now classifiers' performance was similar for all predictors (0.286 to 0.328 for HCVA, 0.541 to 0.296 for 2.5% LCVA, and 0.666 to 0.177 for color vision) (Table 5).

Discussion

In this study, we have analyzed the functional impact of acute ON on vision 6 months after onset, analyzing visual acuity, retinal thickness, visual fields, and quality of vision. We found that while good recovery from ON is evident in terms of HCVA, this is not the case for LCVA, color vision, and the quality of vision, and patients remain significantly impaired. Therefore, our results support the concept that most patients recover poorly from ON, and as such, the development of an effective treatment for acute ON would help prevent such future impairment, which currently represents a significant unmet medical need.[2–4] Visual impairment after 6 months was correlated with early markers of neuroaxonal injury in the retina: RNFL and GCIPL thickness. Since the change in RNFL and GCIPL thickness in the first month was correlated with LCVA and color vision performance at the end of the acute phase of ON,[13] our results suggest that monitoring the early retinal damage by OCT is a feasible strategy to assess the functional prognosis in clinical practice. Moreover, imaging markers based on the pRNFL and GCIPL thickness could help identify the most informative study population for clinical trials testing neuroprotective or regenerative drugs.

Predictors of visual impairment following ON were previously derived from the Optic Neuritis Treatment Trial, which included HCVA LogMAR $\geq +0.4$, contrast sensitivity < 1.0 log units, and visual field mean deviation ≤ -15 dB at baseline or 1 month after onset.[9] In terms of the contribution of MRI or electrophysiology tests, poor visual outcome may be associated with

Table 3. Correlation of retinal atrophy in the first month measured with SD-OCT at baseline and visual outcomes.

		HCVA (LogMAR)	2.5% LCVA	1.25% LCVA	Color vision
pRNFL	*r*	−0.41155	0.4307	0.34032	0.62624
	p	**0.014**	**0.0098**	**0.0455**	**<0.0001**
	n	35	35	35	35
MV	*r*	−0.46034	0.59076	0.49203	0.76631
	p	**0.0054**	**0.0002**	**0.0027**	**<0.0001**
	n	35	35	35	35
mRNFL	*r*	−0.41238	0.62971	0.62976	0.74389
	p	**0.0262**	**0.0003**	**0.0003**	**<0.0001**
	n	29	29	29	29
GCIPL	*r*	−0.38632	0.65784	0.55503	0.75919
	p	**0.0385**	**0.0001**	**0.0018**	**<0.0001**
	n	29	29	29	29
INL	*r*	−0.06796	0.10848	−0.06407	−0.02605
	p	0.7261	0.5754	0.7413	0.8933
	n	29	29	29	29
OPL-ONL	*r*	0.15233	−0.3495	−0.39321	−0.28302
	p	0.4302	0.0631	0.0348	0.1368
	n	29	29	29	29

HCVA: high-contrast visual acuity; LCVA: low-contrast visual acuity; pRNFL: peripapillary retinal nerve fiber layer; mRNFL: macular RNFL; GCIPL: ganglion cell and inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer; MV: macular volume.
The results are expressed as the *r* value, *p* value, and sample size (*n*) of the Spearman correlation between the change from baseline to 1 month later of each retinal layer thickness. Significant results are highlighted in bold.

Table 4. Predictors of visual impairment in ON.

Linear regression models	R^2	Standardized B	95% CI	*p* value
HCVA (LogMAR)	0.2856			0.0126
pRNFL		−0.33247	−0.00371 to 0.00009	
MSD		−0.34720	−0.02542 to 0.00012	
2.5% LCVA	0.5414			0.0002
GCIPL		0.34660	−2.50598 to 34.18043	
INL		0.24442	−10.26966 to 101.96851	
mRNFL		0.45553	2.40492 to 55.47502	
1.25% LCVA	0.4575			0.0004
mRNFL		0.52084	11.69758 to 50.37862	
MSD		0.26975	−0.25166 to 2.72912	
Color vision	0.6656			<0.0001
mRNFL		0.46792	1.61049 to 8.97747	
GCIPL		0.41724	1.44192 to 11.68479	

ON: optic neuritis; HCVA: high-contrast visual acuity; LCVA: low-contrast visual acuity; MSD: mean standard deviation; pRNFL: peripapillary retinal nerve fiber layer; mRNFL: macular RNFL; GCIPL: ganglion cell and inner plexiform layer; INL: inner nuclear layer; CI: confidence interval; DMTs: disease-modifying therapies.
Linear regression models to evaluate the role of retinal thickness change from baseline to month 1 and the MSD of the visual fields at baseline in ON eyes as predictors of the permanent visual impairment 6 months later. The results represent 95% CIs, beta coefficients, and *p* values from the linear regression models that include the following as covariates: sex, age at inclusion, disease duration, and the use of DMTs at baseline.

more extensive or intra-canalicular lesions in orbital MRI lower VEP amplitude or worse initial visual impairment, although such results were mixed and would require replication.[10] The length of the T2

Table 5. Predictors of visual impairment in ON after adjustment for vision at baseline.

Linear regression models	R^2	Standardized B	95% CI	*p* value
HCVA (LogMAR)	0.3277			0.0057
pRNFL		0.26689	−0.00129 to 0.01069	
MSD		0.44727	0.01265 to 0.09303	
2.5% LCVA	0.2955			0.0105
INL		0.29332	−11.14195 to 149.83640	
MSD		−0.42640	−4.73168 to −0.53038	
Color vision	0.1771			0.0362
pRNFL		−0.42088	−21.81427 to −0.79493	

ON: optic neuritis; HCVA: high-contrast visual acuity; LCVA: low-contrast visual acuity; MSD: mean standard deviation; pRNFL: peripapillary retinal nerve fiber layer; mRNFL: macular RNFL; GCIPL: ganglion cell and inner plexiform layer; INL: inner nuclear layer; CI: confidence interval; DMTs: disease-modifying therapies.
Linear regression models to evaluate the role of retinal thickness changes from baseline to month 1 and the MSD of the visual fields at baseline in ON eyes as predictors of the visual impairment 6 months later (change from baseline to month 6). The baseline predicted variables were entered into the analyses as confounders (dependent variables). The results represent 95% CIs, standardized beta coefficients, and *p* values from the linear regression models that include the following as covariates: sex, age at inclusion, disease duration, the use of DMTs at baseline, and the predicted variable at baseline.

lesion and the contrast-enhancing lesion of the optic nerve visualized by MRI has been proposed as a prognostic factor of visual recovery after ON,[11] whereas functional magnetic resonance imaging (fMRI) tests can detect abnormalities associated with visual complaints after ON.[12] Regarding visual fields, we found that the MSD was a predictor of the HCVA, but we believe it does not imply causality but just association. In our previous study with perimetry analysis, we have found that MSD is quite sensitive to diffuse damage in MS.[23] Therefore, we believe that this association is due to the ability to capture diffuse retinal damage, which is the most common in ON as well as influencing HCVA. However, the usefulness of such tests in clinical practice is limited due to their low predictive value. In addition to such low accuracy, the effort of performing MRI and VEP may be an additional burden for many medical centers. Indeed, SD-OCT offers the advantage of being a quick and well-tolerated test that is available at most clinical centers, and its accuracy in measuring changes in GCIPL thickness provides the opportunity to use SD-OCT as a marker of visual impairment soon after ON onset. Previous studies using time domain OCT in ON also found significant association between RNFL thinning and visual acuity, color vision, perimetry, and amplitudes of the VEP.[24]

Recent phase 2 clinical trials in patients with acute ON provides important lessons regarding the relationship between time from clinical onset to therapeutic intervention (therapeutic window), baseline variables, and clinical outcomes. Treatment with anti-Lingo mAb i.v. (BIIB033) in patients with ON randomized in the first 28 days after onset showed efficacy in improving VEP latencies but not in preventing retina atrophy measured by OCT or improving LCVA (NCT01721161). Due to the mechanism of action, intended to promote remyelination, it was expected efficacy in the latencies of VEP and not a direct neuroprotection of the RGCs, but secondary protection (due to remyelination) was not observed as well as lack of clinical efficacy. In the phenytoin trial, patients were recruited in the first 14 days after clinical onset and they observed efficacy in preventing retina atrophy (GCIPL) suggesting a truly neuroprotective effect (NCT01451593).[25] However, such biological effects were not paralleled by improvement of vision. However, such lack of clinical efficacy may be due to the use of not very sensitive outcomes, compared to the most sensitive metrics such as the inter-eye asymmetry of 2.5% LCVA.[26] Amiloride trial in ON included patients in the first 4 weeks after disease onset and failed to show clinical efficacy and signs of neuroprotection (NCT01802489). The fingolimod trial in ON used RNFL as primary endpoint but was terminated prematurely due to the low recruitment process, and no conclusions can be drawn (NCT01757691). Finally, two trials testing erythropoietin in ON has been conducted (NCT00355095 and NCT01962571). Whereas the first trial recruited patients in the first 28 days after clinical onset, current trial has reduced the inclusion window to 10 days. Patients treated with Epo showed an improvement in the MSD of the visual fields, prevention of retina atrophy (RNFL), and improvement of VEP latencies, although such benefits were not consistent across trials and clinical benefits were not

observed.[27–29] The overall experience from such trials is that time from onset to recruitment seems to be critical and there is the trend to reduce it to 10 days. Second, selection of the primary endpoint depends on the drug's mechanism of action. For this reason, OCT (GCIPL or pRNFL) is the priority for neuroprotective drugs, whereas latencies of VEP are more sensitive for remyelinating drugs. Finally, independent of the power of the study, in order to support the usefulness of a drug in development for ON, a trend for the improvement of clinical endpoints (e.g. asymmetry of the 2.5% LCVA) should be observed in parallel to the improvement of the primary (surrogate) endpoint in phase 2 trials.

There are currently several ongoing clinical trials evaluating neuroprotective or remyelinating drugs for ON, offering the promise that new therapeutic strategies will become available to prevent visual dysfunction in ON.[30] A biomarker that readily identifies subjects at high risk of permanent visual impairment at an early stage is essential for these studies, as these patients would represent a treatable target population with a favorable benefit risk balance. In line with other studies, our results suggest that monitoring the change in the GCIPL and pRNFL thickness is the predictor of visual dysfunction measured by LCVA, color vision, and quality of vision.[5,13,31] As discussed above, timing is crucial and interventions should be done early. Even more, ON should be considered as an emergency in the same way than stroke or retinal detachment. Ideally, a biomarker should be highly informative at presentation. This suggests that it will be important to refine the role of OCT markers in the early stages of neuroaxonal damage during ON. As OCT is an accessible, fast, and comfortable technique, physicians would now be able to personalize disease management in order to improve the patient's QoL.

A potential limitation of our study was that patients were not systematically assessed for longer than 6 months, although previous studies have shown that improvements after such time are minor.[8] Furthermore, although we controlled for a prior diagnosis of MS, which may imply diffuse damage or subclinical ON, we did not perform a specific analysis for idiopathic ON as opposed to clinically isolated syndrome (CIS) or relapsing-remitting multiple sclerosis (RRMS) due to the small sample size in each subgroup. In this study, we did not perform a systematic analysis of VEPs, although they were performed on an individual patient basis as part of their diagnosis. Finally, our strategy for identifying statistical predictors of clinical scales at 6 months to be used in the clinical practice prioritized the use of quantitative and easy-to-administer tests such as OCT and perimetry. For this reason, we have not included the clinical scale at baseline and then assess how much added value the paraclinical tests provided to the predictor. Moreover, other statistical modeling approaches as suggested in APOSTEL guideline can provide results with slightly different results.

In summary, our study supports the concept that visual recovery is generally poor following ON and that OCT can be used to predict impaired visual recovery by monitoring the change of GCIPL and pRNFL thickness.

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