Optic Nerve Lesion Length at the Acute Phase of Optic Neuritis Is Predictive of Retinal Neuronal Loss

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Abstract

Background and Objectives

Acute optic neuritis (ON) is a classical presenting symptom of multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), and anti–MOG-associated disorders. The resulting visual impairment is variable and can be severe. Clinicians are in need of predictive biomarkers to optimize the management of acute ON. In this longitudinal study (IRMANO, NCT03651662), we evaluated the ability of optic nerve lesion length measured on MRI at the acute phase of ON to predict retinal neuro-axonal loss and visual impairment at a chronic stage.

Methods

We conducted a longitudinal study (IRMANO, NCT03651662) of patients who presented a clinical episode of ON (≤ 8 weeks). All patients underwent a retinal optical coherence tomography (OCT) and a brain/optic nerve MRI, including 3D double-inversion recovery (DIR) sequence at the acute phase of ON and 12 months later. Primary outcomes were optic nerve DIR hypersignal lesion length, macular ganglion cell–inner plexiform layer (GCIPL) volume measured on OCT, and low-contrast monocular visual acuity (LCMVA).

Results

The study group included 51 patients (33 women, mean age of 32.4 years $\pm$ 7.9). We recruited patients with a clinically isolated syndrome (n = 20), a relapsing-remitting MS (n = 23), an isolated ON (n = 6), and a first clinical episode of NMOSD (n = 2). Optic nerve DIR hypersignal was observed in all but 1 symptomatic optic nerves. At inclusion, the mean optic nerve lesion length (in mm) was 12.35 $\pm$ 5.98. The mean GCIPL volume (in mm^3) significantly decreased between inclusion (1.90 $\pm$ 0.18) and M_{12} (1.67 $\pm$ 0.21; $p < 0.0001$). Optic nerve lesion length at inclusion was significantly associated with GCIPL thinning (estimate $\pm$ SD; -0.012 ± 0.004; $p = 0.0016$) and LCMVA at M_{12} (0.016 $\pm$ 0.003; $p < 0.001$). Optic nerve lesion length significantly increased at M_{12} (15.76 $\pm$ 8.70; $p = 0.0007$). The increase in optic nerve lesion length was significantly associated with the GCIPL thinning between inclusion and M_{12} (-0.012 ± 0.003; $p = 0.0011$).

Discussion

At the acute phase of ON, optic nerve lesion length is an imaging biomarker predictive of retinal neuro-axonal loss and chronic visual impairment, which can help to stratify future therapeutic strategies in acute ON.

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Glossary

3D-DIR = 3D double-inversion recovery; **Abs** = aquaporin 4 antibodies; **ANCOVA** = analysis of covariance; **CIS** = clinically isolated syndrome; **DMT** = disease-modifying therapy; **FU** = follow-up; **GCIPL** = ganglion-cells–inner plexiform layer; **IETD** = intereye retinal thickness difference; **INL** = inner nuclear layer; **LCMVA** = low-contrast monocular visual acuity; **MME** = microcystic macular edema; **MOGAD** = MOG-associated disorder; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **OCT** = optical coherence tomography; **ON** = optic neuritis; **pRNFL** = peripapillary retinal nerve fiber layer; **RRMS** = relapsing-remitting multiple sclerosis; **VF** = visual field.

Classification of Evidence

This study provides Class I evidence that optic nerve lesion length measured on MRI during the acute phase of a first episode of ON is associated with long-term retinal neuro-axonal loss and visual impairment.

Acute optic neuritis (ON) is a classical presenting symptom of multiple sclerosis (MS) where it accounts for 25% of first demyelinating events. Occurrence of ON during the disease is approximately 70%.[1] ON is also one of the most frequent clinical manifestations of neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein–associated disorders (MOGAD). It could also be idiopathic.[2]

Some therapeutic strategies can be proposed in acute ON, including corticosteroids, plasmapheresis, and IV immunoglobulins. Most studies have not demonstrated that the timing of steroid administration makes a long-term visual difference after ON, but some studies suggested that timing of relapse treatment, as corticosteroids administration, may be important in NMOSD.[3,4] In addition, some therapeutics that may promote remyelination are under evaluation.[5] Clinicians are searching for predictive and reliable biomarkers to develop new therapeutic algorithms and to optimize the management of acute ON.

Optic nerve MRI is challenging but remains a performing tool to detect optic nerve involvement in demyelinating diseases. To detect acute ON lesion with MRI, the best diagnostic strategy is by using T2-weighted sequences including both water and fat suppression.[6] Among sequences including water and fat suppression, 3D double-inversion recovery (3D-DIR) sequence is one of the most sensitive.[7,8] With such a sequence, we were able to detect many asymptomatic optic nerve lesions in clinically isolated syndrome[9] (CIS) and MS.[10,11] Diagnostic accuracy of 3D-DIR sequence for the detection of demyelinating optic nerve lesion(s) is very high,[7] and intraobserver and interobserver agreement are very good for optic nerve DIR hypersignal length measurement.[10] At a chronic stage, optic nerve DIR hypersignal has been associated with lower ganglion cell–inner plexiform layer (GCIPL) volumes and higher visual impairment.[10,11] However, the predictive value of optic nerve DIR hypersignal length measured at the acute phase has not been evaluated yet.

Optic nerve lesion length or optic nerve gadolinium enhancement length has been previously suggested as a potential predictive biomarker of visual impairment,[12-14] notably in NMO,[3,15] but other studies did not confirm such results or did not show findings that may support this hypothesis.[16-21]

The aim of this study is to evaluate the association between the length of the optic nerve lesion measured on MRI during the acute phase of a first episode of ON and the long-term retinal neuro-axonal loss and visual impairment.

Methods

IRMANO study (Imagerie par Résonance Magnétique au stade Aigu de la Névrite Optique; NCT03651662) was a longitudinal and prospective cohort study conducted between February 2016 and February 2020, which enrolled 51 patients at Lille MS center (France).

Participants

Consenting adults (aged 18–65 years) diagnosed with a history of acute ON in the last 8 weeks were prospectively recruited. ON diagnosis was made on the basis of suggestive clinical symptoms (loss of vision and dyschromatopsia) and abnormal neuro-ophthalmologic examination, including visual-evoked potentials (P100 latency increasing) and visual fields (VFs; VF defect) if the demyelinating disease was not known. If the patient already experienced an already known demyelinating disease of the CNS, such as MS according to McDonald revised 2017 criteria,[22] NMOSD according to 2015 International consensus criteria,[23] or MOGAD,[24] ON diagnosis was made on the basis of typical clinical symptoms[2] by a senior neurologist specialized in the management and treatment of CNS demyelinating diseases for more than 2 years and subsequently confirmed by a neuro-ophthalmologist. Patients with a unilateral history of ON may be included, but recent acute ON must concern the fellow eye. Included patients presented with a recent clinical episode of acute ON. Data on sex, age at ON onset, type of demyelinating disease, disease duration, and delay between first visual symptoms and inclusion in the study were collected. Some patients were already under disease-modifying therapy (DMT) at the time of MRI/optical coherence tomography (OCT) evaluation. Some others started a DMT during the follow-up (FU). Data on DMT and particularly on fingolimod initiation during the study were collected because

Figure 1 Optic Nerve MRI Findings in a Patient With CIS
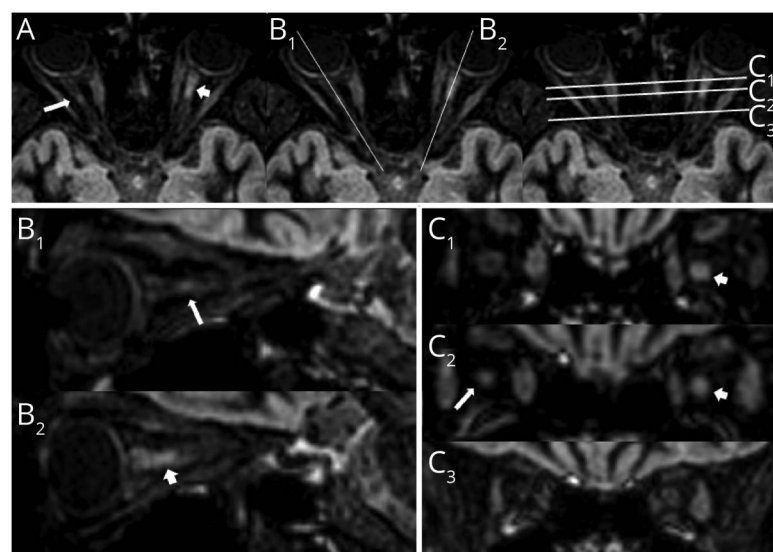
(A) Patient with CIS presenting a left clinical episode of acute optic neuritis. A symptomatic optic nerve lesion (arrowhead) and a right asymptomatic optic nerve lesion (white arrow) were detected on 3D-Double-Inversion Recovery MR sequence. MRI reconstruction of left and right optic nerves showing symptomatic (arrowheads) and asymptomatic (white arrows) lesions in sagittal optic nerve planes (B) and coronal planes (C). CIS = clinically isolated syndrome

fingolimod treatment can lead to increased macular volume in MS.[25] Subjects with other retinal pathology and/or severe ametropia (≥6 diopters) were excluded. Patients with acute ON in an eye with a history of ON were excluded. Recent or ongoing corticosteroid treatment was not an exclusion criterion.

Standard Protocol Approvals, Registrations, and Patient Consents

This study (IRMANO; NCT03651362) was approved by our local ethical committee of Lille University Hospital. Written informed consent was obtained for all participants. Subjects' consent was obtained according to the Declaration of Helsinki.

Data Acquisition and Analysis

Each patient underwent a brain MRI examination at inclusion (M_0) and at 12 months (M_{12}). Brain MRI were performed on a 3-T MRI (Achieva; Philips, Best, The Netherlands) with the use of a 32-channel array head coil. Brain MRI protocol included a 3D-DIR MR sequence with the following parameters: sagittal acquisition, voxel size ($1.2 \times 1.2 \times 1.3$ mm), TR 5500, TE 252, TI Dual 625/2,600, NEX 2, fat suppression SPIR, matrix size 208×208, FOV $250 \times 250 \times 195$, number of slices 300, and sense 2. During the 3D-DIR acquisition, patients were asked to close their eyes and avoid eye movements as much as possible. Signal abnormality was defined as increased signal intensity within the optic nerve compared with the normal white matter signal intensity. To exclude partial volume contamination and to avoid uncertainty on the differentiation of the nerve from the meningeal sheath, optic nerve DIR hypersignal was identified on multiple planes (Figure 1, A–C). Detection of demyelinating lesions on optic nerve/chiasma/optic tracts was performed by a consensus reading of 3D-DIR sequences by 2 trained investigators (M.D. and O.O.) who were blinded to clinical and OCT data. The presence/absence of

DIR hypersignal was recorded for not only each symptomatic nerve but also asymptomatic optic nerves. We defined 5 lesion locations: orbital, canalicular, cisternal, chiasmal, and optic tract. MRI at inclusion and MRI at M_{12} were analyzed independently. Length of optic nerve DIR hypersignal was manually measured directly on MRI workstation.[10] If more than 1 hypersignal was present on 1 nerve, length was defined as the sum of the length of each hypersignal regardless of the presence of gadolinium enhancement.

The group of eyes with acute ON will be considered as eyes with acute ON group. Fellow eyes will be categorized into 3 other groups: an eye group that already presented an ON (eyes with a history of ON), another eye group without a history of ON but with asymptomatic optic nerve lesion (eyes with asymptomatic optic nerve lesion), and another group without a history of ON and without asymptomatic optic nerve lesion (eyes without optic nerve lesion).

OCT examination with a spectral Domain-OCT (Spectralis, Heidelberg Engineering, Germany) was conducted on the same day as MRI (inclusion and M_{12}) and at M_3 also. Our OCT protocol included a peripapillary scan for measuring peripapillary retinal nerve fiber layer (pRNFL; 12°, 3.4 mm circular scan around the optic nerve with a minimum of 50 automatic real time) respecting OSCAR-IB criteria[26] and a macular scan consisting of 25 vertical scans centered on the fovea (a minimum of 25 automatic real time). A macular segmentation was performed with HEYEX software (multilayer segmentation algorithm, Heidelberg Engineering, version 6.0.0.3). The mean volume (Early Treatment Diabetic Retinopathy Study 6 mm disc) was calculated for the macular ganglion cells layer coupled to macular inner plexiform layer (GCIPL) and for the inner nuclear layer (INL). Best-corrected

Table 1 Demographics of the Whole Cohort and Different Patients' Subgroups

	Whole cohort	Patients' subgroups			
	All (n = 51)	CIS (n = 23)	RRMS (n = 20)	NMOSD (n = 2)	Isolated ON (n = 6)
Sex (F/M)	33/18	17/6	10/10	2/0	4/2
Age	32.43 ± 7.89	33.43 ± 8.10	31.20 ± 7.44	35.50 ± 15.59	31.67 ± 5.25
Mean (±SD) disease duration in mo	20.94 ± 54.04	0.35 ± 0.48	50.30 ± 77.36	0.50 ± 0.58	8.83 ± 19.23
Number of patients with a history of ON (%)	5 (9.8%)	0 (0%)	4 (10%)	0 (0%)	1 (8.3%)
Mean (±SD) delay between first visual symptoms and inclusion (in wk)	2.80 ± 1.99	2.04 ± 1.44	3.65 ± 2.08	5.00 ± 3.46	2.17 ± 1.40
Number of patients under fingolimod at inclusion (%)	2 (3.9%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
Number of patients under fingolimod at M12 (%)	5 (9.8%)	0 (0%)	5 (25%)	0 (0%)	0 (0%)

Abbreviations: CIS = clinically isolated syndrome; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; RRMS = relapsing-remitting multiple sclerosis.

low-contrast monocular visual acuity (2.5%; LCMVA) was measured with printed scales (PRECISION-VISION n°2180) in LogMAR unit, at inclusion, M_3, and M_{12}.

Statistical Analysis

A sample size of 51 patients will have 80% power to detect a negative strong correlation between optic nerve lesion length at the acute phase of ON and retinal neuro-axonal loss at 12 months (H0: r = −0.585 vs H1: r = −0.8)[10] with a 0.05 2-sided significance level and taking into account 10% of nonanalyzable data.

Qualitative variables were reported as frequency (percentage) and continuous variables as mean ± SD in case or normal distribution or median (first quartile [Q1]–third quartile [Q3]) otherwise. Normality was assessed graphically and using the Shapiro-Wilk test. Volume change of GCIPL was measured as a difference between value at M_0 and value at M_{12}. Because of clinical or subclinical papillary edema occurring at the acute phase of ON, thickness change of pRNFL was measured as a difference between value at M_3 and value at M_{12}. Volume change of INL was measured as a difference between value at M_0 and value at M_{12}.

Associations of length and topography of the optic nerve lesion assessed at the acute phase of ON with retinal neuro-axonal loss, retinal remodeling process, and visual impairment at 12 months (treated as dependent variables into models) were assessed using analysis of covariance (ANCOVA) adjusted for predefined confounders (retinal thickness/volume at baseline, delay between first visual symptoms and inclusion in the study, initiation of fingolimod treatment during the prospective 12-month FU). Residual normality of ANCOVA models were checked by examining the Quantile-Quantile plots.

A comparison in length of optic nerve lesion length between inclusion and at 12 month assessments was performed using Wilcoxon signed rank test. Associations at the chronic stage (M_{12}) of optic nerve lesion length with retinal layer volumes (treated as dependent variables into models) were studied

using univariable linear regression models. Residual normality of linear regression models were checked by examining the Quantile-Quantile plots. All statistical tests were conducted at the two-tailed α level of 0.05 using SAS software, release 9.4 (SAS Institute, Cary, NC).

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Population

We recruited 51 patients presenting with an acute episode of ON. Among them 23 patients exhibited a CIS suggestive of MS, 20 a clinically definite relapsing-remitting multiple sclerosis (RRMS), 2 a first event of NMOSD (seropositive for antiaquaporin 4 antibodies [Abs]) and 6 an isolated ON. No patient with isolated ON presented anti-MOG Abs. Four patients with RRMS and 1 patient with isolated ON had already presented a clinical ON episode of the fellow eye. One patient with RRMS presented a bilateral acute episode of ON. This patient showed negative results for anti-aquaporin 4 and anti-MOG Abs and presented typical clinical and MRI features of MS.[22] Demographic and clinical characteristics of our cohort are summarized in Table 1.

In Table 2, we summarized the MRI, OCT, and contrast vision characteristics according to the different eyes' subgroups: eyes with acute ON (n = 52), eyes with a history of ON (n = 5), eyes with asymptomatic optic nerve lesion(s) (n = 7), and eyes without a history of ON and without optic nerve lesion (n = 38). We found a symptomatic optic nerve DIR hypersignal at inclusion in all but 1 ON eyes. This patient with RRMS patient was suspected of a first right ON episode, but optic nerve MRI at the acute phase or later did not detect any optic nerve lesion, and GCIPL thickness remained absolutely stable during the FU. At baseline, the mean optic nerve lesion length and retinal layers volume were comparable

Table 2 MRI, OCT, and Visual Performance Characteristics of the Cohort and According to Different Eyes' Subgroups, at Inclusion and at 12 Months

			M_0			M_3			M_{12}		
			n	Mean ± SD	Median (Q1–Q3)	n	Mean ± SD	Median (Q1–Q3)	n	Mean ± SD	Median (Q1–Q3)
Eyes with acute ON (n = 52)	MRI	Length	51	12.35 ± 5.98	11.20 (8.85–14)	—	—	—	50	15.76 ± 8.70	13.00 (10.3–20)
	OCT	GCIPL	52	1.90 ± 0.18	1.91 (1.78–2.015)	43	1.69 ± 0.20	1.69 (1.56–1.82)	50	1.67 ± 0.21	1.68 (1.54–1.81)
		pRNFL	52	109.31 ± 28.94	102 (93–115)	43	87.64 ± 13.82	89 (80.5–98)	50	83.52 ± 14.28	87.5 (75–93)
		INL	52	0.96 ± 0.07	0.97 (0.91–1.01)	43	0.98 ± 0.08	0.97 (0.91–1.04)	50	0.98 ± 0.08	0.985 (0.91–1.04)
	Vision	LCMVA	46	0.96 ± 0.22	1.1 (0.8–1.1)	43	0.78 ± 0.23	0.76 (0.56–1.05)	50	0.69 ± 0.23	0.62 (0.50–0.80)
Eyes with a history of ON (n = 5)	MRI	Length	5	17.66 ± 10.22	14.8 (14.8–25)	—	—	—	5	14.74 ± 6.66	14.70 (14.60–18.50)
	OCT	GCIPL	5	1.76 ± 0.14	1.76 (1.74–1.77)	5	1.77 ± 0.15	1.76 (1.75–1.81)	5	1.78 ± 0.14	1.77 (1.73–1.81)
		pRNFL	5	82.6 ± 5.59	84 (83–86)	5	82.00 ± 6.04	83 (82–85)	5	82.40 ± 4.83	84 (83–85)
		INL	5	1.01 ± 0.13	0.96 (0.94–0.98)	5	0.99 ± 0.13	0.93 (0.93–0.98)	5	0.98 ± 0.12	0.93 (0.92–0.99)
	Vision	LCMVA	5	0.66 ± 0.26	0.60 (0.58–0.64)	5	0.57 ± 0.18	0.66 (0.50–0.66)	5	0.47 ± 0.04	0.50 (0.44–0.50)
Eyes with asymptomatic optic nerve lesions (n = 7)	MRI	Length	7	8.00 ± 2.31	8.1 (7–9.4)	—	—	—	7	7.90 ± 2.63	7.30 (6.95–9.55)
	OCT	GCIPL	7	1.98 ± 0.16	2.01 (1.86–2.09)	5	2.03 ± 0.14	2.04 (1.98–2.11)	7	1.95 ± 0.15	1.90 (1.85–2.05)
		pRNFL	7	96.14 ± 3.76	97 (93.50–98.50)	5	95.20 ± 3.27	96 (95–96)	7	94.71 ± 3.55	95 (92–97)
		INL	7	0.99 ± 0.07	0.99 (0.95–1.03)	5	0.97 ± 0.06	0.97 (0.95–1.02)	7	0.98 ± 0.05	0.98 (0.96–1.02)
	Vision	LCMVA	7	0.47 ± 0.08	0.50 (0.43–0.53)	5	0.59 ± 0.12	0.56 (0.50–0.68)	7	0.59 ± 0.12	0.54 (0.50–0.69)
Eyes without a history of ON and without optic nerve lesions (n = 38)	MRI	Length	—	—	—	—	—	—	—	—	—
	OCT	GCIPL	38	1.93 ± 0.13	1.92 (1.84–2.03)	32	1.92 ± 0.14	1.89 (1.81–2.04)	36	1.93 ± 0.15	1.9 (1.86–2.05)
		pRNFL	38	98.24 ± 11.87	98.5 (91.25–107.75)	32	96.78 ± 11.15	98.50 (91.75–101.75)	36	98.14 ± 12.00	98.5 (90–105)
		INL	38	0.94 ± 0.06	0.93 (0.9–0.97)	32	0.94 ± 0.06	0.93 (0.91–0.98)	36	0.95 ± 0.06	0.98 (0.96–1.02)
	Vision	LCMVA	34	0.57 ± 0.16	0.57 (0.46–0.69)	32	0.58 ± 0.14	0.54 (0.50–0.685)	36	0.56 ± 0.16	0.54 (0.50–0.69)

Abbreviations: GCIPL = ganglion-cells–inner plexiform layer; INL = inner nuclear layer; LCMVA = low-contrast monocular vision acuity (2.5%); OCT = optical coherence tomography; pRNFL = peripapillary retinal nerve fiber layer.
Values are reported as mean ± SD and median (first quartile [Q1]–third quartile [Q3]). LCMVAs (2.5%) are indicated in LogMAR unit.

Figure 2 Flowchart of IRMANO Cohort and the Corresponding Eyes' Subgroups According to the Occurrence of an Acute ON, ON History, and Optic Nerve MRI Data
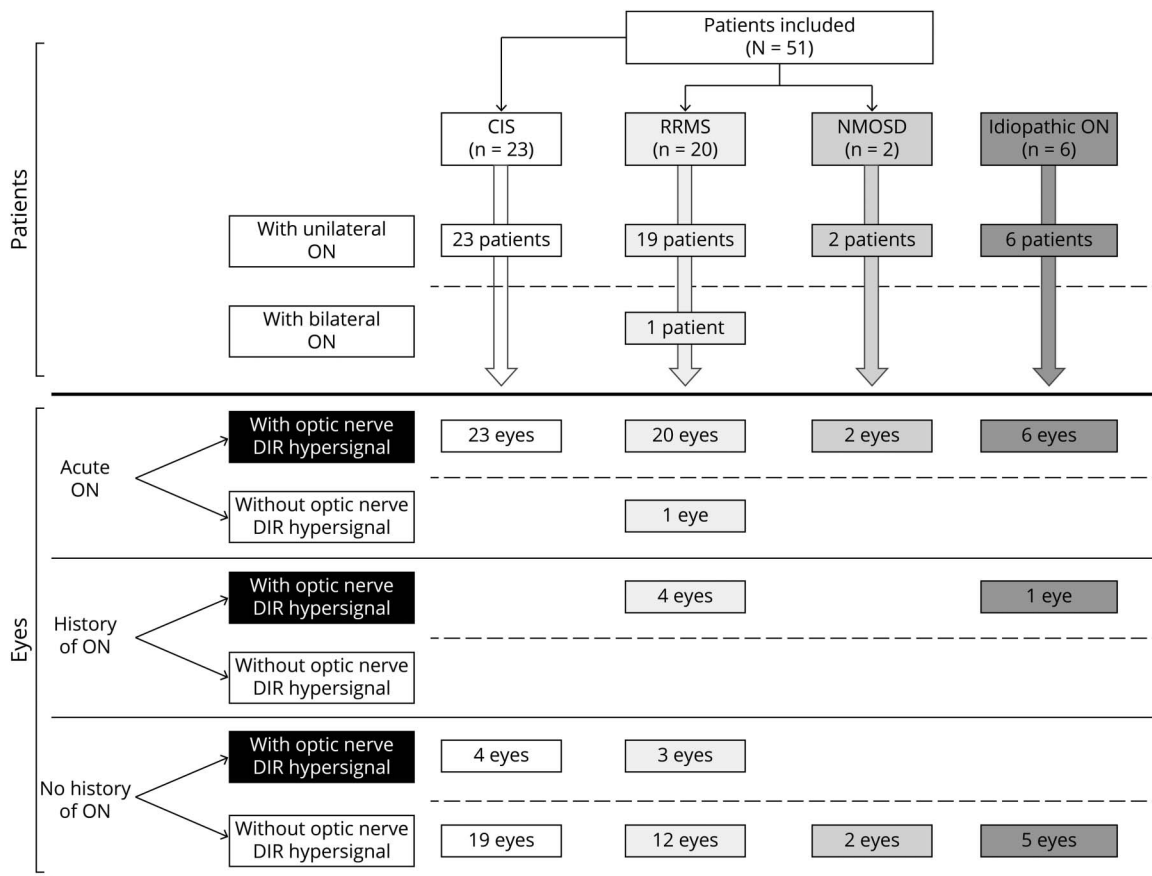
The authors recruited 51 patients presenting an acute episode of ON. One patient with acute ON did not present any optic nerve lesion on MRI. One patient with RRMS presented a bilateral acute ON. All eyes with a history of ON presented an optic nerve lesion. Some patients with CIS and RRMS presented an asymptomatic optic nerve lesion on the fellow eye. CIS = clinically isolated syndrome; DIR = double-inversion recovery; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; RRMS = relapsing-remitting multiple sclerosis.

between CIS-RRMS and NMOSD-ION groups (eTable 1, links.lww.com/NXI/A696).

Gadolinium enhancement was observed in 33 eyes presenting acute ON (63.5%). We found an optic nerve DIR hypersignal in all the 5 eyes with a history of ON (4 RRMS and 1 ION). Among the 45 eyes without a history of ON, we found an asymptomatic optic nerve DIR hypersignal in 7 cases (4 patients with CIS and 3 with RRMS). All optic nerve lesions detected at inclusion were also observed at M_{12}. The flowchart of our cohort is reported on Figure 2. At baseline, we detected 2 optic nerve lesions among 7 ON eyes (4 patients with CIS and 3 with RRMS). The length of these 2 lesions was added. No patient presented any new clinical episode of ON during the 12-month FU period. We did not observe any microcystic macular edema (MME) at baseline or during the FU period on OCT.
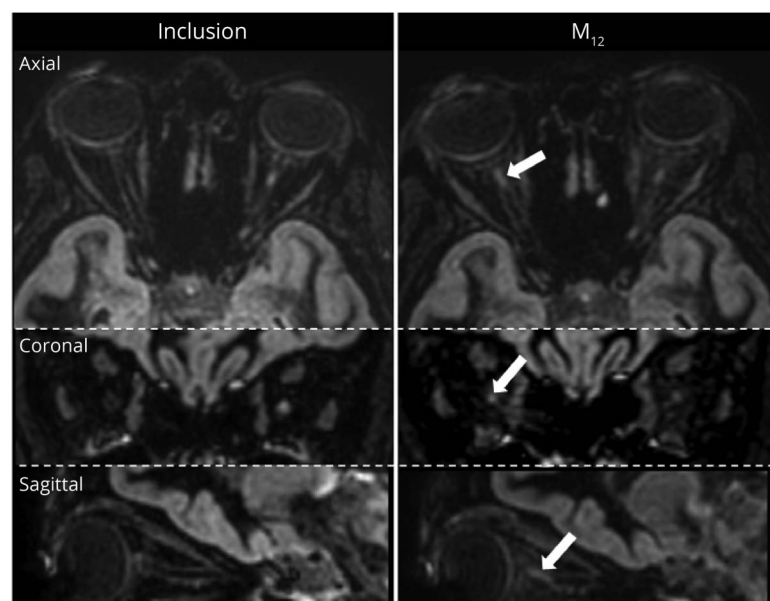
One patient with CIS presented a novel asymptomatic right optic nerve lesion at 12 months (Figure 3). GCIPL volume of this eye without optic nerve lesion at inclusion slightly decreased between inclusion (1.92 mm^3) and M_{12} (1.88 mm^3).

Among all patients, 5 patients with MS (9.8%) were under a DMT. Among them, 2 were treated by beta interferon, 2 by glatiramer acetate, and 1 by fingolimod for more than 1 year. Four patients initiated fingolimod during the study. None of these patients presented any macular edema. All patients received corticosteroid infusions before or at the time of their inclusion. All patients with NMOSD were additionally treated with plasmatic exchanges. Two patients (1 patient with RRMS and 1 with CIS) were lost on FU at M_{12}.

Association Between Optic Nerve Lesion Length at the Acute Phase of Optic Neuritis and Retinal Changes and Chronic Visual Impairment

We found significant association between optic nerve lesion length measured at inclusion and GCIPL volumes decrease between inclusion and M_{12} (estimate ± standard error; -0.012 ± 0.004; $p = 0.0016$) (Table 3). This means that each millimeter of optic nerve lesion length measured at the acute phase of ON is associated with a GCIPL volume decrease of 0.012 mm^3 at the 12-month FU. We also found significant association between optic nerve lesion length and INL

Figure 3 Optic Nerve MRI of a CIS Patient With Detection of a New Asymptomatic Optic Nerve Lesion During the Follow-up

Optic nerve MRI of a patient with CIS presenting a left acute optic neuritis. At inclusion, no lesion was detected on the right optic nerve. At M_{12}, a new right asymptomatic retrobulbar optic nerve DIR hypersignal was detected (white arrows). CIS = clinically isolated syndrome.

volume increase between inclusion and M_{12} or LCMVA measured at M_{12}. We did not find any association between optic nerve lesion length at inclusion and pRNFL decrease. If we focused only on patients experiencing RRMS or CIS, we found comparable results. We observed a trend toward significance between optic nerve lesion length and INL thickening. Results are summarized in Table 3.

Association Between Optic Nerve Lesion Location at the Acute Phase and Retinal Neuro-Axonal Loss and Visual Impairment

Involvement of the different parts of the optic nerve in the whole cohort and different eyes' subgroups is summarized in Table 4. Among acute ON eyes, orbital involvement was observed in 36 patients (69.2%), canalicular involvement in 21 patients (40.4%), cisternal involvement in 13 patients (25%), and chiasmal involvement in 2 patients (3.8%). We did not report any involvement of the optic tracts. No association was observed between any optic nerve lesion site and the GCIPL thinning. However, we found significant association between cisternal optic nerve involvement and a greater pRNFL thinning ($M_3 - M_{12}$; $p = 0.034$). Indeed, we found significant association between involvement of the orbital part at inclusion and a lower visual impairment at M_{12} ($p = 0.027$). At the opposite, we found significant association between involvement of the cisternal part at inclusion and higher visual impairment at M_{12} ($p = 0.014$). No association was observed for any other location (canalicular, chiasma, and optic tracts).

Evolution of Optic Nerve Lesion Length

Considering eyes with acute ON, the mean optic nerve lesion length significantly increased between inclusion (12.35 ± 5.98) and M_{12} (15.76 ± 8.70; $p = 0.0007$). The increase in optic nerve lesion length was significantly associated with the GCIPL thinning between inclusion and M_{12} (−0.012 ± 0.003; $p = 0.0011$).

Considering eyes with asymptomatic optic nerve lesion and eyes with a history of ON together or separately, the optic nerve lesion length was stable between inclusion and M_{12} ($p = 0.25$ for together, $p = 0.61$ for asymptomatic optic nerve lesion, and $p = 0.31$ for eyes with a history of ON).

Association Between Optic Nerve Lesion Length and Retinal Layers Volumes at the Chronic Stage (M_{12})

We observed significant association between the optic nerve lesion length measured at M_{12} and retinal layer volume at M_{12} or chronic visual impairment. The higher was the extent of optic nerve lesion, the higher were the retinal neuro-axonal loss, the retinal remodeling, and the chronic visual impairment. Results are close to our previous studies and summarized in eTable 2, links.lww.com/NXI/A696.

Classification of Evidence

This study provides Class I evidence that optic nerve lesion length measured on MRI during the acute phase of a first episode of ON is associated with long-term retinal neuro-axonal loss and visual impairment.

Discussion

We found that optic nerve lesion length measured at the acute phase of ON is a predictive biomarker of retinal neuro-axonal loss and visual impairment at a chronic stage. We also showed that optic nerve lesion length at the acute phase is associated with retinal remodeling process (INL thickening) and that it

Table 3 Associations Between ON Lesion Length Measured at the Acute Phase and Retinal Layer Changes Between Inclusion and at 12 Months or Chronic Visual Impairment at 12 months

	Whole acute ON eyes cohort (n = 52)			Acute ON eyes cohort of CIS and MS (n = 44)		
	Estimate	Standard error	*p* Value	Estimate	Standard error	*p* Value
GCIPL volume change (mm^3)	−0.012	0.004	**0.0016**	−0.013	0.004	**0.0011**
pRNFL thickness change (μm) at M$_{12}$	+0.036	0.156	0.82	−0.024	0.152	0.87
INL volume change (mm^3)	+0.002	0.001	**0.0263**	+0.002	0.001	0.0846
LCMVA 2.5% at M12	+0.016	0.003	**<0.0001**	+0.014	0.005	**0.0056**

Abbreviations: CIS = clinically isolated syndrome; GCIPL = ganglion-cells–inner plexiform layer; INL = inner nuclear layer; LCMVA = low-contrast monocular vision acuity (2.5%); MS = multiple sclerosis; ON = optic neuritis; pRNFL = peripapillary retinal nerve fiber layer.
LCMVA (2.5%) are indicated in LogMAR unit.
Significant *p* values (≥0.05) are indicated in bold.

slightly increased during the FU. Furthermore, the increase in optic nerve lesion length during the FU was associated with a greater retinal neuro-axonal loss and visual impairment.

We showed significant association between optic nerve lesion length at the acute phase and both structural and functional visual parameters. Thus, we clearly suggest that the optic nerve lesion length in acute ON can be considered as a predictive biomarker of retinal neuro-axonal loss, retinal remodeling process, and visual impairment. The greater is the optic nerve lesion length, the higher is the GCIPL thinning, INL thickening, and chronic visual impairment. After an ON episode, INL thickening is classical and may, in most severe cases, be associated with the presence of MME. MME is reported in nearly 4% of patients with RRMS and 20% of patients with NMOSD.[27] Similar to others,[18-20,28] we did not observe any association between optic nerve lesion length and pRNFL thinning. Large to very subtle optic nerve swelling is frequently observed at the acute stage of ON.[29] This edema represents a confusing factor that affects and artificially increases the measurement of pRNFL thickness at the acute stage. For this reason, we have planned to measure pRNFL at M$_3$ when papillary edema has disappeared and to evaluate pRNFL atrophy between M$_3$ and M$_{12}$. However, it could be possible that M$_3$ evaluation was already too late to properly assess the pRNFL thinning. GCIPL is not affected by optic nerve inflammation and optic nerve edema and is probably a more accurate and relevant retinal imaging biomarker than pRNFL in neuroinflammatory disorders affecting the optic nerve. GCIPL intereye retinal thickness difference (IETD) is a better marker of asymptomatic optic nerve lesion in CIS than pRNFL IETD,[30] and GCIPL thickness is better correlated to visual impairment than pRNFL.[31] GCIPL thinning after a clinical episode of ON is an early event. Major part of the GCIPL thinning is observed during the first 2 months, and GCIPL thinning during the first month is predictive of short-term (6 months) visual impairment.[32] Despite the value of such a measurement, this early thinning of GCIPL is not strictly applicable at the acute stage of diagnosis as a predictive biomarker because it requires a 1-month FU OCT to predict remote chronic visual impairment.

We did not confirm that canalicular optic nerve involvement was associated with negative visual outcome,[10,12,13,28] but our results suggest that cisternal involvement might be associated with negative visual outcome (higher pRNFL thinning and higher residual visual impairment) and that orbital optic nerve involvement might be associated with lower residual visual impairment. However, such results were not confirmed by GCIPL analysis. Because GCIPL has been shown to be a more

Table 4 Involvement of the Different Parts of the Optic Nerve in the Whole Cohort and Different Eyes' Subgroups

	Involvement of the different parts of the optic nerve, n (%)				
	Orbital	Canalicular	Cisternal	Chiasmatic	Optic tract
All eyes (n = 102)	47 (46.1)	25 (24.5)	16 (15.7)	2 (2)	0 (0)
Eyes with acute ON (n = 52)	36 (69.2)	21 (40.4)	13 (25)	2 (3.8)	0 (0)
Eyes with a history of ON (n = 5)	5 (100)	2 (40.0)	2 (40.0)	0 (0)	0 (0)
Eyes with asymptomatic optic nerve lesions (n = 7)	6 (85.7)	2 (28.6)	1 (14.3)	0 (0)	0 (0)
Eyes without a history of ON and without optic nerve lesions (n = 38)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: ON = optic neuritis.

interesting and reliable OCT outcome parameter than pRNFL and because p values remain close to the statistical threshold, cautiousness is needed when interpreting these results.

If some studies reported that optic nerve lesion length was stable between the acute and chronic phases,[20,21] others reported that optic nerve lesion length increases with time.[13,14,16,33] One study has suggested that shortest lesions at the acute phase increased and longest lesions at the acute phase may decrease.[34] In our cohort, we showed that the length of acute optic nerve lesion significantly increased and that the length of chronic symptomatic or asymptomatic optic nerve lesions was stable. Indeed, we observed that the increase in optic nerve lesion length was significantly associated with the subsequent GCIPL thinning in eyes with acute ON. If at the acute stage of ON, we may associate optic nerve DIR hypersignal with demyelination, our results suggest that the increasing in optic nerve lesion length is at least partly associated with the neurodegenerative process along the optic nerve after an ON episode. This process is bidirectional: anterograde (from the optic nerve lesion to the ipsilateral lateral geniculate nucleus) and retrograde (from the optic nerve lesion to the retina). Indeed, optic nerve DIR hypersignal can be observed in noninflammatory diseases, such as chronic glaucoma[35] and Leber hereditary optic neuropathy.[36] If detected at distance from acute ON or observed on a non-ON eye (NON eye), the extent of optic nerve lesion on MRI should probably be considered as the consequence of a dual process including demyelination and neurodegeneration (axonal loss). According to our results, a progression of the optic nerve lesion length could be useful to assess the efficacy of future neuroprotective drugs in acute ON.

With this new independent prospective cohort, we replicated the previous results of our group showing that optic nerve lesion length at the chronic stage was correlated with the retinal layers volume/thickness and the chronic visual impairment.[10] Thus, optic nerve lesion length is both a predictive biomarker of retinal axonal loss when measured at the acute phase of ON and a biomarker of retinal neuro-axonal loss if measured at a chronic stage of ON or in asymptomatic cases.

We did not observe optic nerve gadolinium enhancement in all affected optic nerves, but some patients might have already received corticosteroids before inclusion, especially in patients with known RRMS. Recent corticosteroid treatment was not an exclusion criterion in our study. In fact, previous studies have shown that corticosteroids did not affect optic nerve lesion length at the acute phase.[3,34] Furthermore, length of optic nerve enhancement seems not different between patients with or without corticosteroids.[28] In addition, some symptomatic optic nerve lesions were quite short, making more difficult detection of gadolinium enhancement.

In neuroinflammatory diseases and more particularly in MS, neurodegenerative process along the optic pathways is considered to be transsynaptic with an anterograde (from the retina to the cortex) and retrograde (from the cortex to the retina) manner and to be the consequence of demyelinating lesions on optic nerves, chiasma, optic tracts, and optic radiations.[11] In our analysis, we did not adjust to the T2 lesion burden within the optic radiations because previous works from our group suggested the lack of association between optic radiation lesion volume and retinal layer volumes in CIS[9] and RRMS.[11] In addition, we included patients presenting with ION and NMOSD who did not present any significant asymptomatic T2 brain lesions.

In this study, we confirmed that 3D-DIR MRI sequence is sensitive for the detection of demyelinating optic nerve lesions by detecting all but 1 acute symptomatic optic nerve lesions. This suspected case of acute ON without optic nerve DIR hypersignal and GCPIL thinning might ultimately be considered a posteriori as an overdiagnosis of ON. If patients with MS referred to Neuro-Ophthalmologic unit for acute ON are more likely to experience ON, up to 4% may present an overdiagnosis of ON.[37] In this study, we showed again that asymptomatic optic nerve lesions are frequent in CIS and RRMS. Conversely, and as previously reported,[10] this was not observed in patients with ION or NMOSD from our cohort. Detection of asymptomatic optic nerve lesion might be helpful both for the positive diagnosis of MS (i.e., future MS diagnosis criteria) and for differential diagnosis. Its presence may be supportive of MS diagnosis. In this study, evolution of the length of symptomatic and asymptomatic optic nerve lesions differs, suggesting that asymptomatic lesions are stable and older than symptomatic ones. Thus, we suggest that the presence of asymptomatic optic nerve lesions in CIS/RRMS might be representative of dissemination of disease in time[38] and it might also be considered as a marker of dissemination in space.[39,40]

Our study has some limitations. First, we did not perform a complete neuro-ophthalmologic examination at M_{12} and evaluated only chronic visual impairment with a low-contrast visual acuity chart. Regardless of the study protocol, a complete neuro-ophthalmologic examination had been performed at 3–4 months. Post hoc complementary analysis is warranted. Second, multiple optic nerve lesions were detected on some symptomatic eyes, and we cannot exclude that such optic nerves may cumulate both symptomatic and asymptomatic lesions, especially in patients with CIS and RRMS. We acknowledge that it may represent a bias in our analysis, but these patients with multiple but unilateral optic nerve lesions are representative of the real-life practice. On the whole, one-third of patients with CIS/RRMS experienced asymptomatic optic nerve lesions.[9,11] Indeed, presence or absence of gadolinium enhancement is not sufficient to distinguish a recent active lesion from a chronic one. Excluding eyes with multiple lesions from our analysis would have reduced the power of our statistical analysis. We preferred to stick to real-life practicing and to consider the worse-case scenario by adding the different lengths. Third, our cohort may seem as quite heterogeneous because we included patients with various causes of ON and did not focus only on cases with CIS and MS.

However, OCT and MRI data of ON eyes at baseline were similar between CIS-RRMS and NMOSD-ION subgroups, and our results remained comparable when focusing only on CIS and RRMS. Finally, we could not exclude false-positive findings regarding multiple comparisons, but our study is exploratory, and we cannot certify that each symptomatic or asymptomatic optic nerve hypersignal corresponds to a demyelinating lesion and not to a lesion of another type.

Optic nerve MRI still remains a challenge, and interscanner variability remains an additional difficulty in applying optic nerve lesion length as an imaging biomarker, but sensitive optic nerve MRI sequence for detecting demyelinating lesion in routine are more and more developing. If it seems better to perform a 3D MRI sequence for measuring optic nerve lesion length, this remains feasible and reliable on a coronal 2D MRI sequence. Optic nerve MRI is important for the diagnosis of ON, helpful for identifying the underlying demyelinating disease,[2] and provides a promising imaging biomarker able to predict visual impairment and retinal changes at the acute phase of ON. The optic nerve lesion length should be taken into account in future algorithms for therapeutic management of acute ON.

Disclosure
The authors report no disclosures. Go to Neurology.org/NN for full disclosures.

Appendix Authors

Name	Location	Contribution
Mickael Denis, MD	University of Lille, France	Analysis and interpretation of the data; drafting and revising the article for intellectual content
Jean-Philippe Woillez, MD, PhD	University of Lille, France	Major role in the acquisition of data
Vasily M. Smirnov, MD	University of Lille, France	Analysis and interpretation of the data; drafting and revising the article for intellectual content
Elodie Drumez	University of Lille, France	Design and conceptualization of the study; analysis of the data

Appendix (continued)

Name	Location	Contribution
Julien Lannoy, MD	University of Lille, France	Revising the article for intellectual content
Julie Boucher, MD	University of Lille, France	Revising the article for intellectual content
Mickael Zedet, MD	University of Lille, France	Revising the article for intellectual content
Jean-Pierre Pruvo, MD, PhD	University of Lille, France	Revising the article for intellectual content
Julien Labreuche	University of Lille, France	Design and conceptualization of the study; analysis of the data
Helene Zephir, MD, PhD	University of Lille, France	Analysis and interpretation of the data; drafting and revising the article for intellectual content
Xavier Leclerc, MD, PhD	University of Lille, France	Analysis and interpretation of the data; drafting and revising the article for intellectual content
Olivier Outteryck, MD, PhD	University of Lille, France	Design and conceptualization of the study; acquisition of data; analysis and interpretation of the data; drafting and revising the article for intellectual content; and study supervision

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