Optical Coherence Tomography : A window to the optic nerve in clinically isolated syndrome

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BACKGROUND [1]

IN **MULTIPLE SCLEROSIS** (MS):

- ✓ PERIPAPILLARY RETINAL NERVE FIBER LAYER (PRNFL), MACULAR INNER RETINAL LAYERS ATROPHY AND INNER NUCLEAR LAYER THICKENING IS CLASSICALLY DESCRIBED AFTER THE OCCURRENCE OF A **CLINICAL EPISODE OF OPTIC NEURITIS (ON)**

- ✓ HOWEVER, RETINAL ATROPHY MAY ALSO BE FOUND IN **MS EYES WITHOUT HISTORY OF CLINICAL ON**

IN **CLINICALLY ISOLATED SYNDROME** (CIS), THE EARLIEST CLINICAL STAGE OF MS:

- ✓ OCT STUDIES HAVE REPORTED (ASYMPTOMATIC) RETINAL ATROPHY **IN ABSENCE OF CLINICAL EPISODE OF ON**

IN ABSENCE OF CLINICAL EPISODE OF ON, RETINAL ATROPHY WOULD BE THE CONSEQUENCE OF A RETROGRADE TRANS-SYNAPTIC NEURODEGENERATIVE PROCESS RELATED TO DEMYELINATING LESIONS WITHIN OPTIC RADIATIONS AND VISUAL CORTICAL ATROPHY

OCT MAY BE A WINDOW TO THE BRAIN.

Background [2]

Subclinical Optic Nerve involvement has never been evaluated by optic nerve MRI or electrophysiology

Only one OCT study focusing on CIS looked for asymptomatic optic nerve involvement

(Oberwahrenbrock et al., 2013)

- ✓ 45 patients with CIS matched to healthy controls
- ✓ VEPs coupled to OCT at 8.6 months (± 12.1m) after CIS, but no optic nerve MRI performed
- ✓ In absence of symptomatic (detected clinically) and asymptomatic involvement (detected on VEPs), the CIS subgroup of patients still presented a retinal atrophy vs the healthy controls.

Main Objective

To evaluate the association between asymptomatic optic nerve demyelinating lesion in patients presenting a clinically isolated syndrome and the asymptomatic retinal neuro-axonal loss previously reported at the CIS stage.

Is retinal neuro-axonal loss previously reported at CIS stage due to missed subclinical optic nerve demyelinating lesions on MRI ?

Methods

CINOCIS

A Prospective study, June 2013- July 2017 (CHRU Lille)

Population

Patients with typical CIS ≤ 4.5 months ; 18-65 yo.

Subjects with other retinal pathology (e.g. glaucoma, uveitis, surgery, traumatism) or severe ametropia (≥ 6 dioptres) were excluded.

Multiparametric Evaluation

2.5–4.5 months after CIS (on the same day):

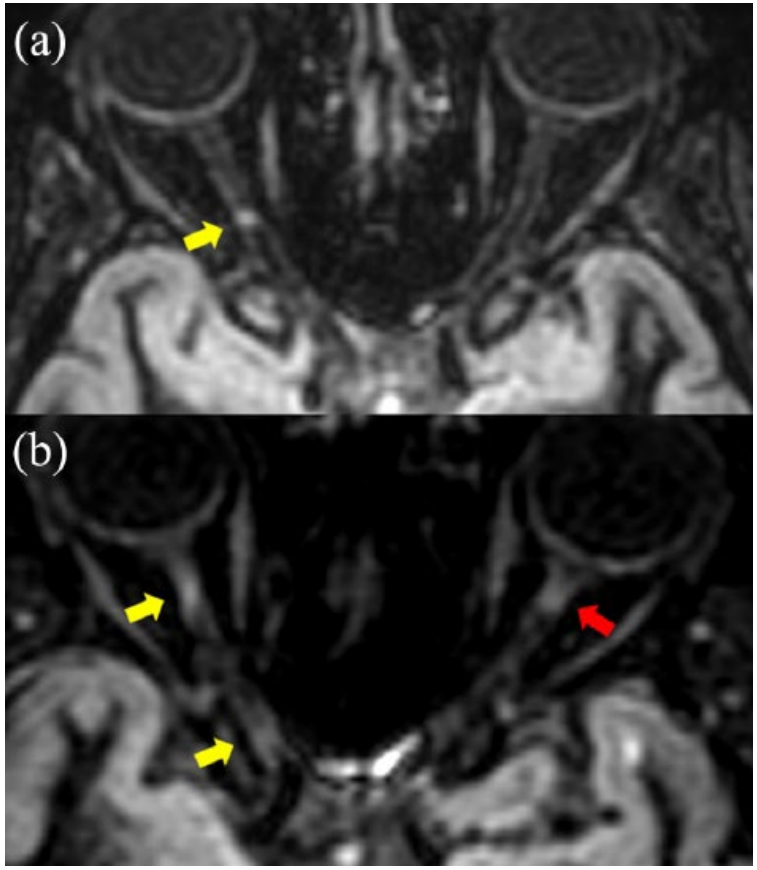
- ✓ Clinical examination + low contrast monocular visual acuity (LCMVA)
- ✓ MRI (3T): 3D-T1, 3D-FLAIR, 3D-DIR (brain + optic nerves), 3D-T1 Gd
- ✓ OCT analysis

OCT analysis

CIS patients were matched (1:1) to healthy control subjects according to age and gender (HC were selected from the local healthy control OCT database).

MRI PROTOCOL

(A) & (B) OPTIC NERVE HYPERSIGNAL ON AXIAL 3D-DIR MRI



London et al., MSJ 2018

OPTIC NERVES WERE STUDIED ON 3D-DOUBLE INVERSION RECOVERY (DIR) SEQUENCE

- ✓ PRESENCE/ABSENCE OF DIR HYPERSIGNAL
- ✓ NUMBER OF DIR HYPERSIGNAL
- ✓ TOTAL LENGTH OF DIR HYPERSIGNAL

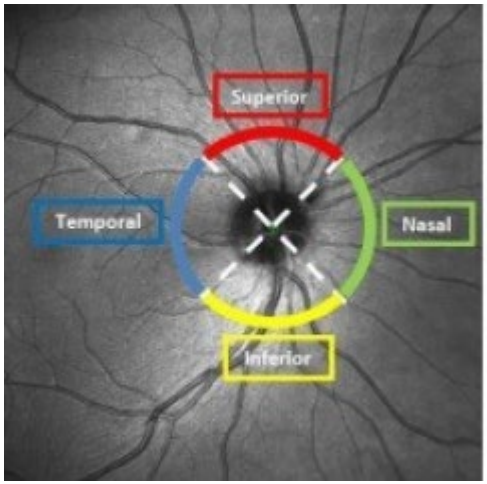
VOLUME OF T2 LESIONS WITHIN THE OPTIC RADIATIONS

VOLUME OF THE PRIMARY VISUAL CORTEX (SEGMENTED ON 3D-T1-FFE SEQUENCE WITH FREESURFER)

EACH VOLUME WAS NORMALIZED IN RELATION TO THE INTRACRANIAL VOLUME

OCT ANALYSIS

REGION OF THE PERIPAPILLARY RING SCAN

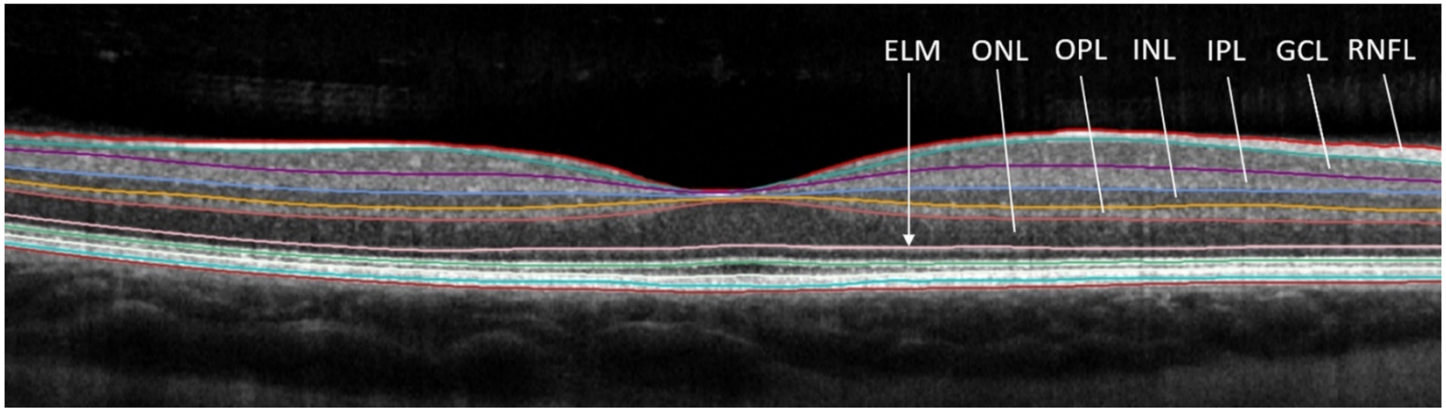


FOURTH GENERATION SPECTRAL-DOMAIN OCT

(SPECTRALIS, HEIDELBERG ENGINEERING)

PROTOCOL RESPECTING OSCAR-IB CRITERIA (TO GUARANTEE RIGOROUS QUALITY CONTROL)

PERFORMED BY AN EXPERIENCED OCT READER (O.O.)

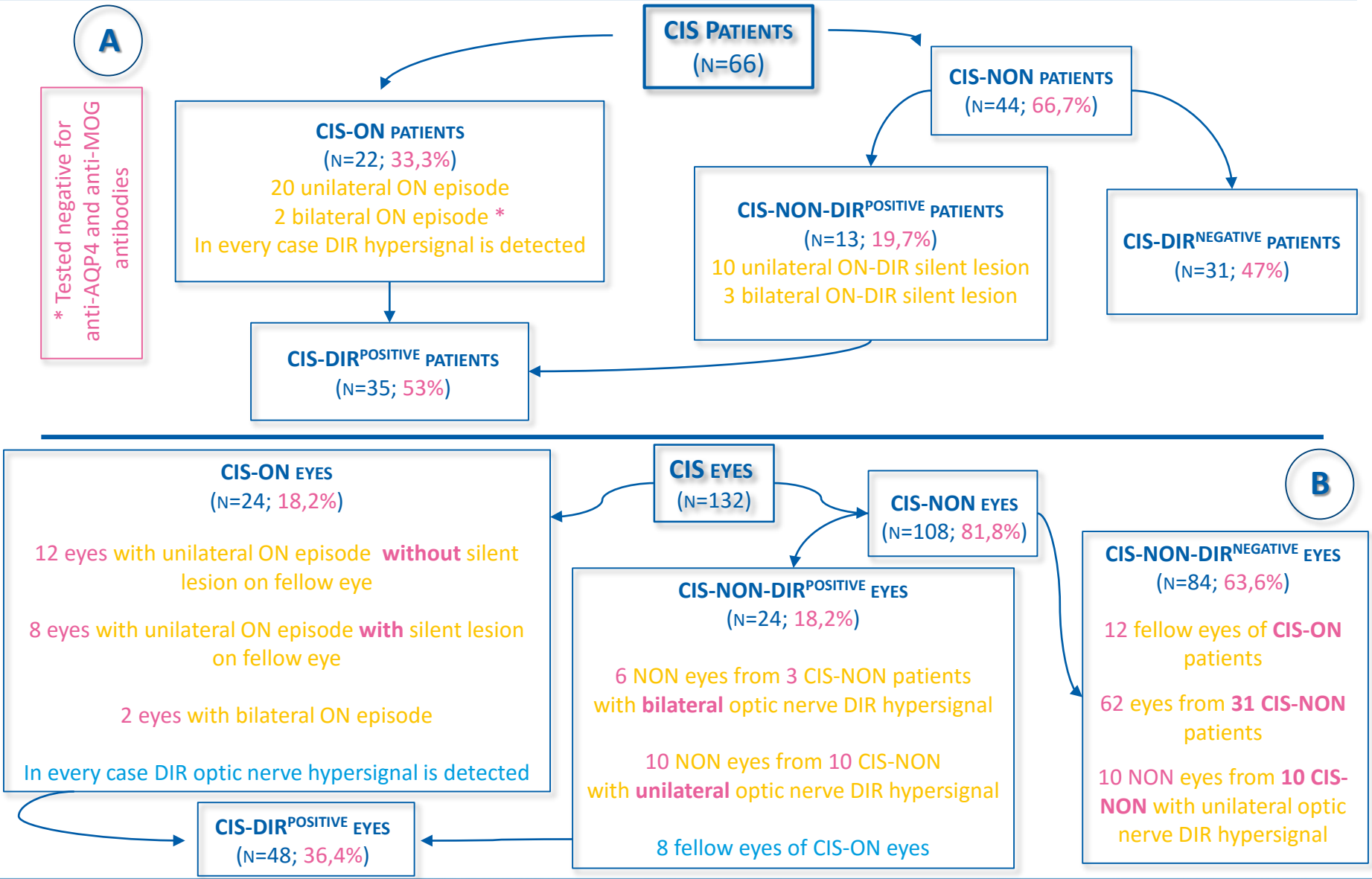


INFL: RETINAL NERVE FIBER LAYER
GCL: GANGLION CELL LAYER
IPL: INNER PLEXIFORM LAYER
mGCIPL
INL: INNER NUCLEAR LAYER
OPL: OUTER PLEXIFORM LAYER
ONL: OUTER NUCLEAR LAYER
ELM: EXTERNAL LIMITING MEMBRANE

MACULAR SCAN DEPICTING THE IDENTIFIED INTRARETINAL LAYERS (OCT HEIDELBERG SPECTRALIS®)

(LAMBE ET AL. Curr Treat Options Neurol 2018)

RESULTS


A
* Tested negative for anti-AQP4 and anti-MOG antibodies
CIS PATIENTS (N=66)
CIS-ON PATIENTS (N=22; 33,3%)
20 unilateral ON episode
2 bilateral ON episode *
In every case DIR hypersignal is detected
CIS-NON PATIENTS (N=44; 66,7%)
CIS-NON-DIR POSITIVE PATIENTS (N=13; 19,7%)
10 unilateral ON-DIR silent lesion
3 bilateral ON-DIR silent lesion
CIS-DIR NEGATIVE PATIENTS (N=31; 47%)
CIS-DIR POSITIVE PATIENTS (N=35; 53%)
B
CIS-ON EYES (N=24; 18,2%)
12 eyes with unilateral ON episode without silent lesion on fellow eye
8 eyes with unilateral ON episode with silent lesion on fellow eye
2 eyes with bilateral ON episode
In every case DIR optic nerve hypersignal is detected
CIS EYES (N=132)
CIS-NON EYES (N=108; 81,8%)
CIS-NON-DIR POSITIVE EYES (N=24; 18,2%)
6 NON eyes from 3 CIS-NON patients with bilateral optic nerve DIR hypersignal
10 NON eyes from 10 CIS-NON with unilateral optic nerve DIR hypersignal
8 fellow eyes of CIS-ON eyes
CIS-NON-DIR NEGATIVE EYES (N=84; 63,6%)
12 fellow eyes of CIS-ON patients
62 eyes from 31 CIS-NON patients
10 NON eyes from 10 CIS-NON with unilateral optic nerve DIR hypersignal
CIS-DIR POSITIVE EYES (N=48; 36,4%)

COMPARISONS OF RETINAL THICKNESS BETWEEN HEALTHY CONTROLS AND CIS EYES SUBGROUPS (1)

Between-groups comparisons	Number (subjects/eyes)	OCT parameters	β (95%CI)	*P*-value
HC versus CIS-ON	(22/44) versus (22/24)	Global pRNFL thickness, µm	−11.85 (−19.23 to −4.48)	**0.003**
		Temporal pRNFL thickness, µm	−18.92 (−24.90 to −12.93)	**<0.0001**
		mGCIPL volume, mm^3	−0.121 (−0.168 to −0.074)	**<0.0001**
		mINL volume, mm^3	0.012 (−0.001 to 0.026)	0.060
		Low contrast monocular vision acuity	−15.2 (−21.4 to −9.2)	**<0.0001**
HC versus CIS-NON	(64/128) versus (64/108)	Global pRNFL thickness, µm	0.20 (−2.69 to 3.09)	0.89
		Temporal pRNFL thickness, µm	−2.70 (−5.97 to 0.57)	0.10
		mGCIPL volume, mm^3	−0.023 (−0.039 to −0.008)	**0.004**
		mINL volume, mm^3	−0.003 (−0.011 to 0.004)	0.37
		Low contrast monocular vision acuity	−4.59 (−6.87 to −2.31)	**0.0001**
HC versus CIS-NON-DIR^{positive}	(21/42) versus (21/24)	Global pRNFL thickness, µm	−2.93 (−8.98 to 3.12)	0.33
		Temporal pRNFL thickness, µm	−8.60 (−14.02 to −3.18)	**0.003**
		mGCIPL volume, mm^3	−0.043 (−0.068 to −0.019)	**0.001**
		mINL volume, mm^3	0.004 (−0.009 to 0.016)	0.53
		Low contrast monocular vision acuity	−5.89 (−11.17 to −0.60)	**0.030**
HC versus CIS-NON-DIR^{negative}	(53/106) versus (53/84)	Global pRNFL thickness, µm	1.38 (−1.77 to 4.53)	0.39
		Temporal pRNFL thickness, µm	−1.29 (−4.92 to 2.34)	0.48
		mGCIPL volume, mm^3	−0.016 (−0.034 to 0.003)	0.083
		mINL volume, mm^3	−0.005 (−0.013 to 0.004)	0.27
		Low contrast monocular vision acuity	−4.29 (−6.65 to −1.92)	**0.0005**

HC
healthy controls

CIS-ON
CIS with history of optic neuritis

CIS-NON
CIS without history of optic neuritis

CIS-NON-DIR POSITIVE
CIS with asymptomatic optic nerve hypersignal

CIS-NON-DIR NEGATIVE
CIS without symptomatic or asymptomatic optic nerve hypersignal

β INDICATES REGRESSION COEFFICIENT ESTIMATED USING LINEAR MIXED MODELS WHICH CORRESPONDS TO THE MEAN BETWEEN-GROUP DIFFERENCE IN RETINAL THICKNESSES/VOLUME.

SIGNIFICANT STATISTICAL VALUES **(P < 0.05)** ARE INDICATED IN **BOLD**.

CI = CONFIDENCE INTERVAL.

COMPARISONS OF RETINAL THICKNESS BETWEEN THE DIFFERENT CIS EYES SUBGROUPS (2)

Between-groups comparisons	Number (subjects/eyes)	OCT parameters	β (95%CI)	*P*-value
CIS-ON versus CIS-NON-DIR^{positive}	(22/24) versus (21/24)	Global pRNFL thickness, µm	4.80 (−1.03 to 10.65)	0.098
		Temporal pRNFL thickness, µm	9.64 (4.58 to 14.70)	**0.001**
		mGCIPL volume, mm^3	0.064 (0.017 to 0.112)	**0.012**
		mINL volume, mm^3	−0.012 (−0.020 to −0.003)	**0.010**
		Low contrast monocular vision acuity	8.16 (0.32 to 15.99)	**0.043**
CIS-NON-DIR^{positive} versus CIS-NON-DIR^{negative}	(21/24) versus (53/84)	Global pRNFL thickness, µm	−2.35 (−4.77 to 0.07)	0.056
		Temporal pRNFL thickness, µm	−3.83 (−8.07 to 0.41)	0.075
		mGCIPL volume, mm^3	−0.019 (−0.032 to −0.006)	**0.005**
		mINL volume, mm^3	−0.0003 (−0.007 to 0.007)	0.94
		Low contrast monocular vision acuity	−3.07 (−6.42 to 0.28)	0.071
CIS-DIR^{positive} versus CIS-NON-DIR^{negative}	(35/48) versus (53/84)	Global pRNFL thickness, µm	9.20 (5.60 to 12.80)	**<0.0001**
		Temporal pRNFL thickness, µm	10.05 (6.33 to 13.77)	**<0.0001**
		mGCIPL volume, mm^3	0.066 (0.044 to 0.089)	**<0.0001**
		mINL volume, mm^3	−0.004 (−0.010 to 0.002)	0.14
		Low contrast monocular vision acuity	8.18 (4.89 to 11.47)	**<0.001**

HC
healthy controls

CIS-ON
CIS with history of optic neuritis

CIS-NON
CIS without history of optic neuritis

CIS-NON-DIR POSITIVE
CIS with asymptomatic optic nerve hypersignal

CIS-NON-DIR NEGATIVE
CIS without symptomatic or asymptomatic optic nerve hypersignal

β INDICATES REGRESSION COEFFICIENT ESTIMATED USING LINEAR MIXED MODELS WHICH CORRESPONDS TO THE MEAN BETWEEN-GROUP DIFFERENCE IN RETINAL THICKNESSES/VOLUME.

SIGNIFICANT STATISTICAL VALUES **(P < 0.05)** ARE INDICATED IN **BOLD**.

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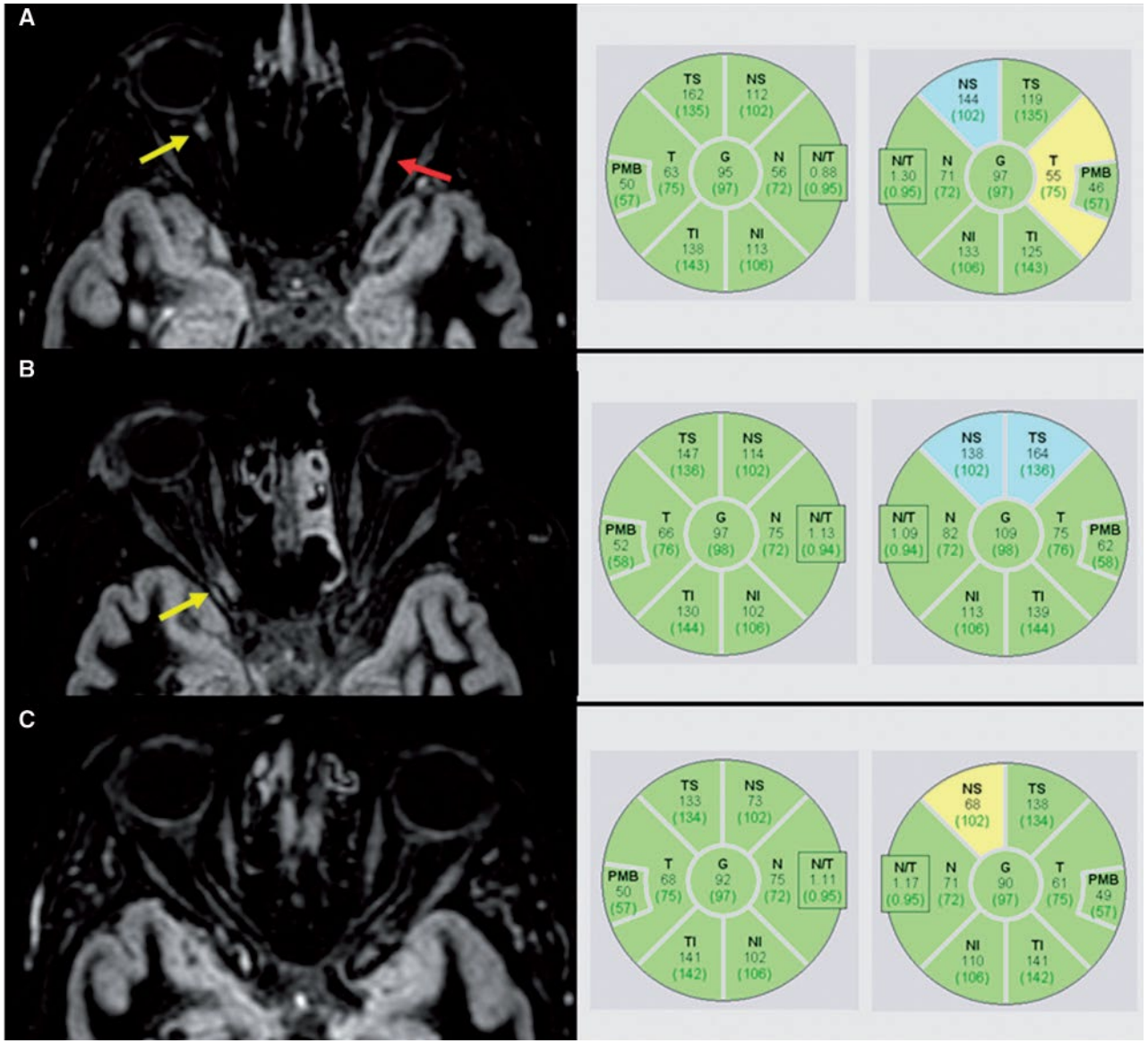

PATIENT (A):

HAD BOTH SYMPTOMATIC AND ASYMPTOMATIC ORBITAL OPTIC NERVE DIR HYPERSIGNAL ;
OCT SHOWED NO ASYMMETRY ON GLOBAL PRNFL.

PATIENT (B):

HAD ONE ASYMPTOMATIC CANALICULAR OPTIC NERVE DIR HYPERSIGNAL ;
OCT SCAN SHOWED SLIGHT ASYMMETRY OF GLOBAL PRNFL.

PATIENT (C):

HAD NO OPTIC NERVE DIR HYPERSIGNAL ;
OCT SHOWED NO ASYMMETRY ON GLOBAL PRNFL.

CONCLUSIONS

- ✓ ASYMPTOMATIC OPTIC NERVE IS FREQUENT AT THE EARLIEST CLINICAL STAGE OF MS (31.8% OF THE WHOLE PATIENT COHORT)

- ✓ ASYMPTOMATIC OPTIC NERVE INVOLVEMENT IS ASSOCIATED WITH RETINAL NEURO-AXONAL LOSS INDEPENDENTLY OF DEMYELINATING LESIONS WITHIN THE OPTIC RADIATIONS AND PRIMARY VISUAL CORTEX VOLUME.

- ✓ ASYMPTOMATIC OPTIC NERVE INVOLVEMENT DETECTED ON OPTIC NERVE MRI AT CIS STAGE APPEARS TO BE THE MAIN CAUSE OF ASYMPTOMATIC RETINAL AXONAL LOSS REPORTED AT CIS STAGE

OCT PERFORMED AT THE EARLIEST CLINICAL STAGE OF MULTIPLE SCLEROSIS SHOULD BE CONSIDERED MORE AS **A 'WINDOW TO THE MULTIPLE SCLEROSIS OPTIC NERVE'** RATHER THAN A "WINDOW TO THE MULTIPLE SCLEROSIS BRAIN"

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Optical coherence tomography: a window to the optic nerve in clinically isolated syndrome

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In this study, we aimed to evaluate the association of asymptomatic optic nerve demyelinating lesion in patients presenting a clinically isolated syndrome with the asymptomatic retinal neuro-axonal loss previously reported at clinically isolated syndrome. We prospectively recruited 66 patients presenting a clinically isolated syndrome and 66 healthy control subjects matched according to age and gender. All patients underwent brain magnetic resonance imaging including 3D-double inversion recovery (DIR) sequence, optical coherence tomography examination and visual function evaluation, at 2.5–4.5 months after CIS. Evaluation criteria were presence and length of optic nerve DIR hypersignal, retinal layers (including ganglion cell inner plexiform layer and inner nuclear layer) thickness/volume, and low contrast monocular vision acuity (number of letters correctly identified). All clinically isolated syndrome eyes with past history of optic neuritis (CIS-ON) presented an optic nerve DIR hypersignal. We observed

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