A longitudinal evaluation of RNFL thickness in Clinically Isolated Syndrome:
RNFL thickness changes and Multiple Sclerosis risk

Chiara Zanetta, Gloria Dalla Costa, Simone Guerrieri, Marco Pisa, Gabriela Girafa, Lucia Moiola, Vittorio Martinelli, Giancarlo Comi, Letizia Leocani

Neurological Dep.t & INSPE - Institute of Experimental Neurology; University Hospital - IRCCS S.Raffaele, Milan – Italy

Introduction

The visual pathway is receiving increasing attention as a reliable model for investigating non invasively demyelination, remyelination and neurodegeneration processes in multiple sclerosis (MS) [1]. As axonal damage occurs since the onset of MS, early diagnosis represents the main purpose of diagnostic criteria and of clinicians in everyday clinical practice [2]. An acute episode of neurologic deficit, known as Clinically Isolated Syndrome (CIS), is a presenting syndrome in 85% of patients who will ultimately develop MS. Known risk factors of conversion to Clinically Definite Multiple Sclerosis (CDMS) in CIS include young age, intrathecal immunoglobulin synthesis (BOIgG) and the presence of high lesion load at disease onset [3]. Optical coherence tomography (OCT) thickness measures of retinal nerve fiber layer (RNFL) and macular measurements including ganglion cell (GCL) layer, inner plexiform layer (IPL) and inner nuclear layer (INL) are used as markers of axonal and neuronal degeneration [4]. The aim of this study is to explore basal characteristics and longitudinal changes in OCT parameters in patients with CIS and evaluate their prognostic value for conversion to CDMS.

Methods

Seventy-four consecutive CIS patients (***Table 1***) underwent OCT at baseline and after a mean follow up of 29.8 (8.60-81.23) months. OCT was performed using a high-resolution spectral-domain device (Heidelberg Spectralis-OCT: Spectralis; Heidelberg Engineering); RNFL was measured with a 3.5 mm standard circle scan protocol centered on the optic disc and a volume scan for the macula was also performed. Thickness was interpreted using a dataset of normal values, normalized according to age and sex, provided by the constructor. Disability, BOIgG and number of T2 hyperintense and gadolinium-enhancing lesion (GD+) at baseline were collected. Each eye was analyzed individually and multilevel mixed effects models were used to explore longitudinal changes in OCT measurements of each eye. Eyes affected by acute optic neuritis (AON) (31) and with ophthalmic disease at baseline (2) were excluded from the analysis and only the contralateral eyes were considered. Eyes which developed AON during follow up (2) were as well excluded. Patients with bilateral presence of one of the previous conditions (1) were excluded from the analysis. Data were corrected considering basal T2 lesion load, age, sex and presence of BOIgG.

CHARACTERISTICS	All patients (n = 74)	CDMS (n = 17)	No MS (n = 57)
Follow up, mean months ± SD	29.8 ± 14.7	32.0 ± 14.3	29.1 ± 14.8
Age at baseline, mean yr ± SD	36.6 ± 9.7	33.5 ± 10.6	37.5 ± 9.3
Sex,			
Females, No. (%)	43 (58.1)	10 (58.8)	33 (57.9)
Males, No. (%)	31 (41.9)	7 (41.2)	24 (42.1)
Type of onset, No. (%)			
optic neuritis	31 (41.9)	8 (47.1)	23 (40.4)
other	43 (58.1)	9 (52.9)	34 (59.6)
Expanded Disability Status Scale score, median (IQ range)	1.5 (1.0-2.0)	1.5 (1.0-2.0)	1.5 (1.0-2.0)
T2 lesions at brain MRI, No. (%)			
0-1	13 (17.6)	3 (17.6)	10 (17.6)
2-9	33 (44.6)	7 (41.2)	26 (45.6)
> 9	28 (37.8)	7 (41.2)	21 (36.8)
Presence of **gadolinium enhancing lesions**, No. (%)	21 (28.3)	6 (35.2)	15 (26.3)
Presence of **gadolinium enhancing** lesions at **optic nerve**, No. (%)	11 (14.9)	5 (29.4)	6 (10.5)
Presence of **CSF oligoclonal bands**, No. (%)	46 (62.2)	16 (94.1)	30 (52.6)

Table 1. *Clinical and demographic data*

Results

Baseline evaluation

Patients who developed CDMS (17%, 8 AON at baseline) were younger, showed higher baseline T2 (41.2 vs 36.8% with > 9 T2 lesions) and GD+ (35.2 vs 26.3%) lesion load and presence of BOIgG (94.1 vs 52.6%) (***Table 1***). Mean baseline RNFL thickness was 94.75 ± 11.78 µm, significantly lower in CIS with GD+ lesions in brain and (asymptomatic) optic nerve and increased EDSS at baseline (p<0.05 in all instances) (***Table 3***).

Longitudinal analysis

Longitudinal changes in RNFL thickness significantly differed between patients who developed CDMS (1) and who did not (0): a mean RNFL decrease of 0.16 µm per month (p<0.001) was observed in converters with respect to non-converters (**Fig. 1**), regardless of basal T2 lesion load, age, sex and BOIgG.

	Univariate analysis				Multivariate analysis		
	Coefficient	95% CIs	p		Coefficient	95% CIs	p
Age at baseline	0.00	-1.9 - 0.20	0.98		-	-	-
Sex, male vs females	- 1.14	-5.04 - 2.77	0.57		-	-	-
Type of onset, optic neuritis vs other	-5.36	-10.00 - -0.72	0.02		- 3.87	-8.38 - -0.65	0.05
EDSS at onset	3.93	0.63 - 7.22	0.02		3.72	0.52 - 6.93	0.02
T2 lesions at brain MRI							
2-9 vs 0-1	-3.27	-8.66 - 2.11	0.23		-	-	-
> 9 vs 0-1	-4.15	-9.69 - 1.38	0.14				
Presence of **gadolinium enhancing** lesions	- 6.95	-11.06 - -2.84	<0.01		-	-	-
Presence of *gadolinium enhancing lesions at the optic nerve*	- 5.10	-10.44 - 0.23	0.06		-	-	-
Presence of **CSF oligoclonal bands**	- 0.65	- 4.69 - 3.39	0.75		-	-	-

Table 2. *Predictors of RNFL thickness at baseline*

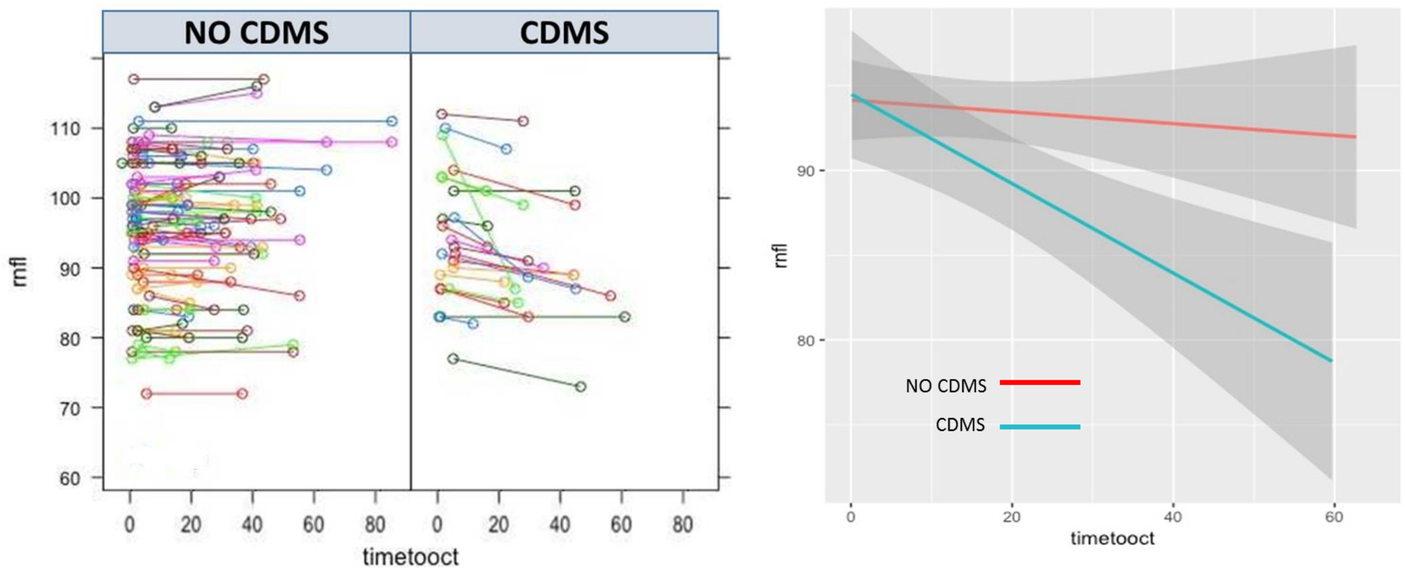

Fig 1. *Exploring RNFL in CDMS converters VS non converters*

Discussion and Conclusions

RNFL thickness may be a useful biomarker for evaluation of neurodegeneration, monitoring of CIS patients and predicting conversion to CDMS. Larger longitudinal studies on CIS patients are needed to confirm our preliminary findings and the utility of OCT in clinical practice.

Bibliography and Acknowledgements

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