Subclinical anterior optic pathway involvement in early multiple sclerosis and clinically isolated syndromes

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Aim of the study

Optical coherence tomography is gaining increasing relevance in the assessment of people with multiple sclerosis. Converging evidence point to the view that neuro-retinal changes, in eyes without acute optic neuritis, reflect inflammatory and neurodegenerative processes taking place throughout the CNS.

The present study aims at exploring the usefulness of optical coherence tomography as a marker of inflammation and disease burden in the earliest phases of the disease.

Methods

Patients receiving an extensive diagnostic evaluation at the IRCCS San Raffaele Hospital for a neurological episode suggestive of an inflammatory CNS disease were asked to participate to a VEP/OCT assessment as part of a prospective observational study in which over 220 patients were enrolled. The present study focuses on those who (1) received a diagnosis of multiple sclerosis or CIS at hospital discharge (Polman, 2011) after alternative diagnoses have been ruled out, (2) agreed to the use of a CSF sample - collected during the clinical workup - for research purposes.

150 patients were enrolled, among those 32 patients had another previous misdiagnosed episode. Participants underwent: contrast-enhanced 1.5 Tesla brain MRI, EDSS, high and low-contrast visual acuity-VA (1,25% and 2,5%), mEPs (MEP, SEP, VEP) with score calculation [Leocani et al 2006], OCT with peripapillary RNFL and macular GCIPL and INL segmentation. All patients had CSF sampling with oligoclonal bands (OCB), microvesicles count (MVs/uL), dosage of a set of cytokine and chemokine (IL1b, IL2, IL4, IL5, IL6, IL7, IL8, IL10, IL12, IL13, IL17, IFNg, TNFa, CCL4, CCL2, GM-CSF, G-CSF). In a subgroup (74 pts) serum neurofilaments have been obtained (Simoa platform). Eyes with acute optic neuritis (50 eyes) were excluded from the analyses. 40 sex and age matched controls were enrolled for the OCT analyses.

Results

Subclinical optic nerve involvement is frequent and associated with disease burden

In patients without prior visual symptoms, VEP conduction abnormalities and OCT asymmetries above published thresholds are frequent. VEP and GCIPL asymmetries are more accurate than pRNFL thresholds.

Importantly, patients with asymptomatic GCIPL asymmetries and VEP abnormalities showed higher: brain MRI lesion load, motor and somatosensory evoked potential abnormalities, frequency of OCB, disease duration, low contrast visual acuity deficits.

The association with several indexes of disease burden further strengthen the hypothesis that the subclinical VEP and OCT abnormalities we found are a meaningful expression of the dissemination of MS pathology.

	Heathy Controls		CIS and CDMS		CIS		CIS w/o McDonald 2010 MS	
	n = 40		n = 90		n = 73		n = 44	
RNFL asymmetry ≥ 5µm, *(1)*	**12.5%**	**5 pts**	**22.2%**	**20 pts**	**17.8%**	**13 pts**	**20.5%**	**9 pts**
RNFL asymmetry ≥ 7µm, *(3)*	5%	2 pts	13.3%	12 pts	9.6%	7 pts	9.1%	4 pts
RNFL asymmetry ≥ 12µm, *(4)*	0%	none	3.3%	3 pts	2.7%	2 pts	2.3%	1 pt
GCIPL asymmetry ≥ 4µm, *(1)*	**0%**	**none**	**12.2%**	**11 pts**	**6.8%**	**5 pts**	**6.8%**	**3 pts**
GCIPL asymmetry ≥ 3µm, *(3)*	2.5%	1 pt	20%	18 pts	13.7%	10 pts	11.4%	5 pts
GCIPL asymmetry ≥ 5µm, *(4)*	0%	none	8.9%	8 pts	5.5%	4 pts	4.5%	2 pts
VEP abnormalities	**2.5%**	**1 pt**	**26.7%**	**24 pts**	**19.2%**	**14 pts**	**18.8%**	**8 pts**

Retinal thickness asymmetry from Nolan-Kenney et al, 2019: (1) cut-off values based on unilateral optic neuritis history (ROC curve analysis); cut-off values based on (3) 95th and (4) 99th percentile of healthy normative data.

GCIPL reflects disease burden occurring beyond the optic nerve

CIS and CDMS (n=90)			
Variable	B value	Chi-square	P value
EDSS (score)	**-0.033**	**4.31**	**0.038**
Disease duration (months)	**-0.011**	**4.82**	**0.038**
LCVA 2.5% (dec)	**+0.021**	**3.87**	**0.049**
LCVA 1.25% (dec)	**+0.032**	**9.23**	**0.002**
Gd enhancing lesions (presence)	**-0.075**	**5.38**	**0.02**
Multimodal EP score	**-0.011**	**5.64**	**0.018**
MEP-SSEP score	**-0.012**	**4.91**	**0.027**
CSF-speficic oligoclonal bands (presence)	**-0.077**	**4.78**	**0.029**
IgG Index (Link)	-0.085	2.81	0.093
Brain T2 lesion load (classes)	-0.029	2.78	0.096

CIS (n=73)			
Variable	B value	Chi-square	P value
Multimodal EP score	**-0.012**	**4.61**	**0.032**
MEP-SSEP score	**-0.013**	**4.82**	**0.028**
CSF-speficic oligoclonal bands (presence)	**-0.079**	**4.12**	**0.042**
LCVA 1.25% (dec)	+0.019	3.26	0.071
Disease duration (months)	-0.035	2.72	0.099

CIS w/o McDonald 2010 MS (n=44)			
Variable	B value	Chi-square	P value
CSF-speficic oligoclonal bands (presence)	-0.091	3.38	0.06

LCVA: low contrast visual acuity; EP: evoked potentials; MEP: motor evoked potentials; SSEP: somatosensory evoked potentials

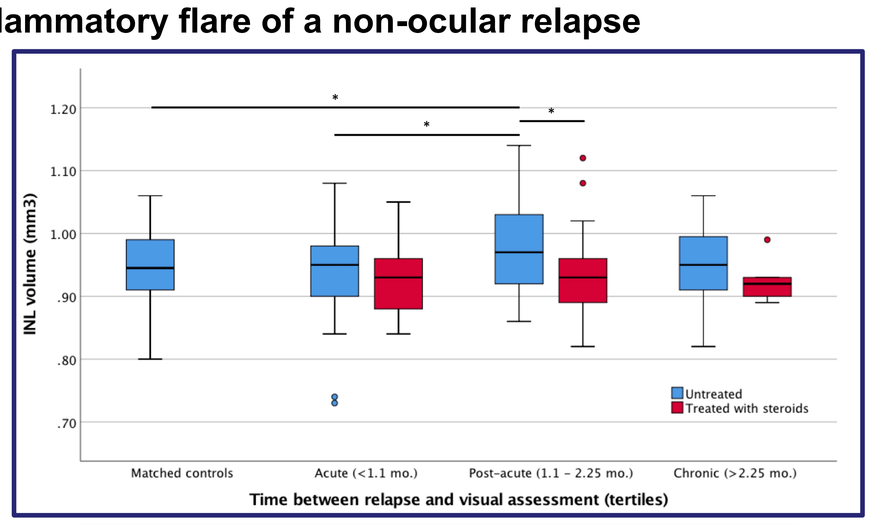
GCIPL is associated with disease burden regardless of detectable optic nerve involvement, even in the earliest phases of the disease. This was probed in a generalized linear model taking into account intra-subject variability, history of prior ON as well as paraclinical evidences of subclinical ON (VEP abnormalities and OCT asymmetries).

These finding suggest the existence of a strong link between retinal and CNS pathology in MS.

INL dynamic suggest that subclinical optic nerve involvement occurs during the inflammatory flare of a non-ocular relapse

We found that 1-3 months after a non-ocular relapse there is an increase in the thickness of the INL, which is counteracted by steroid treatment.

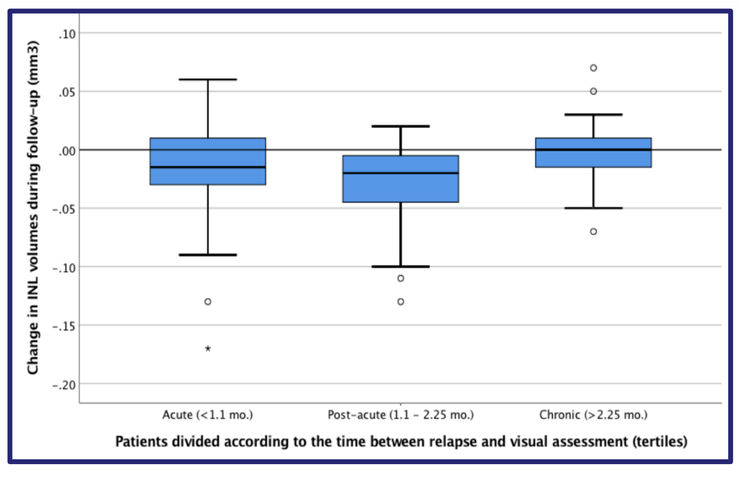
In fact: when stratifying the cohort according to the time from last relapse onset (1st tertile: < 1.1 months; 2nd: 1.1 - 2.25 months; 3rd: >2.25 months). INL swelling occurred in the subacute and chronic phase compared with the acute cohort. Steroid treatment was also associated with lower INL volumes. These finding were confirmed in 65 patients with follow up OCT scan (mean follow-up : 27 +/- 11.91 months) As both the acute (n 26; -0.02 mm3, p=0.021) and the subacute cohort (n 20; -0.036 mm3,, p<0.0001) displayed significant INL thinning during follow-up while no change was detected in the chronic group.



It is known from prior literature that:

1) Ganglion Cell loss occurs 1-2 months after optic nerve involvement (Kupersmith, 2016)
2) Muller cells, which are one of the main cellular components of the INL, respond to GC loss by changing their morphology and physiology in a reparative attempt and this leads to a transient hypertrophy and cellular swelling (Iandiev, 2006)

We hypothesize that during the inflammatory flare there is a subclinical optic nerve involvement which leads to GC loss, Muller cells' response and INL swelling. This hypothesis may also explain the link between retinal neurodegeneration and global disease burden.



Discussion and conclusions

The present study suggests that VEP and OCT evidence of subclinical optic nerve involvement is associated with a greater disease burden in clinically isolated syndrome. Moreover, neuro-retinal changes are present since the earliest phases of the disease and yield important information regarding the neurodegenerative processes occurring in the CNS. The pathogenetic mechanism underpinning strict link between retinal and CNS pathology is still debated, the transient INL swelling we observe suggest the existence of a subclinical optic nerve involvement during the inflammatory flare.