OCT measures are associated with disease burden and inflammatory activity in newly diagnosed MS and clinically isolated syndromes

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Introduction

The features of asymptomatic involvement of optic nerve and retina in early multiple sclerosis (MS) and clinically isolated syndromes (CIS) are still unclear. Ganglion cell – Inner Plexiform thickness (GCIPL) is considered as a marker of neurodegeneration in MS but whether it only reflects subclinical optic neuritis (ON) in early MS needs further elucidation. Recent studies also suggested that inner nuclear layer (INL) thickens during disease activity possibly as a result of Muller cells' dysfunction. We aimed to assess the association between INL thickness and, CSF and clinical measures of inflammatory activity. Moreover, we assessed the prevalence of subclinical optic nerve involvement using both VEP and OCT in a wide cohort of patients prospectively enrolled among those receiving a diagnostic assessment for a neurological episode suggestive of multiple sclerosis.

Methods

We enrolled 150 consecutive patients hospitalized for a neurological episode suggestive of MS. . At hospital discharge the 51.3% reached the McDonald 2010 MS criteria, the 21.3% were clinically defined MS. Patients 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 and retinal involvement assessed using VEP and OCT:

We defined asymptomatic optic nerve involvement as the presence of abnormalities in VEP conduction in eyes without prior history of optic neuritis. We also defined asymptomatic optic neuritis using published thresholds of pRNFL or GCIPL interocular asymmetry (Nolan-Kenney, 2019). Results are displayed in Table 1.

Patients without prior ON history in whom subclinical optic nerve involvement was detected using VEP, displayed a longer disease duration (p=0,02), higher brain lesion load (p=0.01), higher MEP-SSEP score (p=0,004), higher frequency of oligoclonal band (over 90% vs 60%, p=0,005). These data were confirmed after the exclusion of CDMS. Patients with asymptomatic OCT asymmetries only displeyed an increased multimodal evoked potentials' score – which was confirmed after the exclusion of clinically defined MS patients - and a trend toward a higher age and disease duration.

		VEP asymptomatic abnormalities	
Sample		% of patients	% of eyes
CIS and early MS	90 pts (180 eyes)	**26.7**	18.9
CIS - not meeting CDMS criteria	73 pts (146 eyes)	**19.2**	14.4
CIS - not meeting Polman 2011 criteria	44 pts (88 eyes)	**18.2**	12.5
		OCT asymtomatic asymmetries	
Sample		% of patients	% of eyes
CIS and early MS	90 pts (180 eyes)	**25.6**	13.3
CIS - not meeting CDMS criteria	73 pts (146 eyes)	**17.8**	9.6
CIS - not meeting Polman 2011 criteria	44 pts (88 eyes)	**20.5**	11.4

Macular ganglion cell – inner plexiform layer thickness:

In a generalized linear model taking into account intra-subject variability, the history of prior ON as well as paraclinical evidences of prior ON (VEP abnormalities and OCT asymmetries), we confirmed that GCIPL was associated with disease duration, EDSS, low contrast visual acuity (LCVA), brain lesion load, presence of gadolinium (Gd) enhancing lesions, multimodal evoked potentials, presence of oligoclonal bands and Link index regardless of detectable optic nerve involvement.

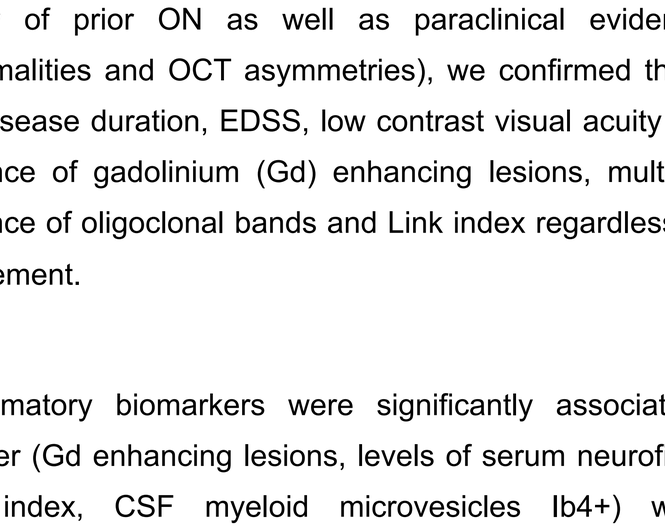
	B value	X^2	P value		B value	X^2	P value
Disease duration (yr)	-0.011	4.82	0.038	*Multimodal EP (score)*	-0.011	5.64	0.018
LVCA 2.5% (dec)	+0.021	3.87	0.049	*MEP - SSEP (score)*	-0.012	4.91	0.027
LVCA 1.25% (dec)	+0.032	9.23	0.002	*Oligoclonal bands (y/n)*	-0.077	4.78	0.029
Brain T2 lesion load (class)	*-0.029*	*2.78*	*0.096*	*IgG Index (Link)*	-0.085	2.81	0.093
Gd enhancing lesions (y/n)	-0.075	5.38	0.020	*EDSS (score)*	-0,033	4,31	0,038

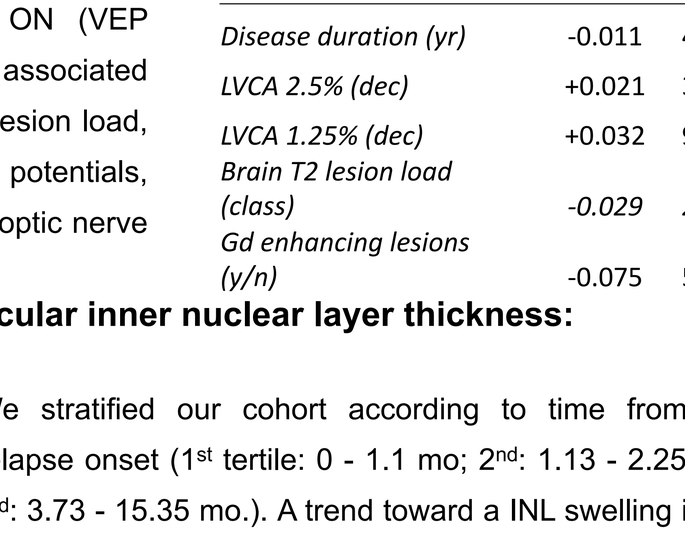
Macular inner nuclear layer thickness:

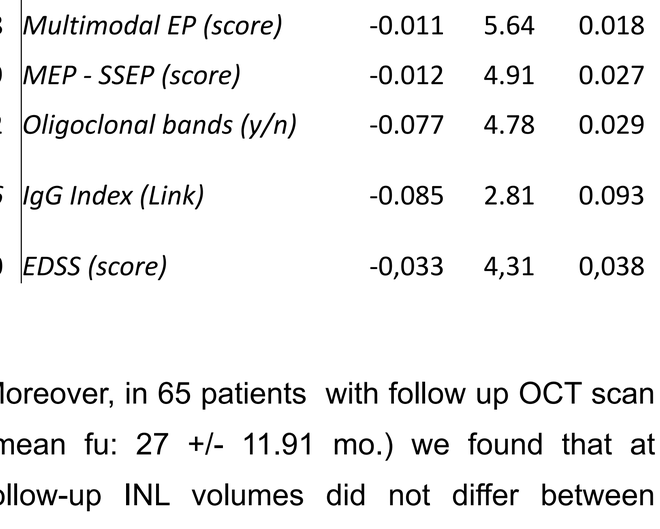
Inflammatory biomarkers were significantly associated one-another (Gd enhancing lesions, levels of serum neurofilaments, Link index, CSF myeloid microvesicles Ib4+) while no association was found with INL volumes. Moreover, patients with a relapse in the month before OCT assessment or with gd enhancing lesions at brain MRI scan (43 pts, 0.948 mm3, CI95% 0.933 – 0.965 mm3) did not significantly differ from healthy controls (40 pts, 0.936 mm3, CI95% 0.922 – 0.95 mm3) or with patients with neither active MRI or recent relapse (< 3 months) (61 pts, 0.935 mm3, CI95% 0.922 – 0.95 mm3; p=0.2).

We stratified our cohort according to time from last relapse onset (1st tertile: 0 - 1.1 mo; 2nd: 1.13 - 2.25 mo.; 3rd: 3.73 - 15.35 mo.). A trend toward a INL swelling in the subacute and chronic phase compared with the acute cohort with a mean difference of +0.024 (p=0.069) and +0.005 (p=0.095) respectively. When excluding steroid treated patients, we found instead that the subacute group was significantly thicker compared with both the acute cohort (mean difference: +0.043, p=0.044) and the healthy control group (mean difference: +0.04, p=0.008).

Moreover, in 65 patients with follow up OCT scan (mean fu: 27 +/- 11.91 mo.) we found that at follow-up INL volumes did not differ between subgroups according to treatment or time from last relapse. Secondly, we found that both the acute (26 pts; -0.02 mm3, CI95% -0.036 to -0.003, p=0.021) and the subacute cohort (20 pts; -0.036 mm3, CI95% -0.055 to -0.018, p<0.0001) displayed significant INL thinning during fu while no change was detected in the chronic group.







Discussion and conclusions

Asymptomatic optic nerve involvement, revealed by OCT and VEP, is frequent in CIS and is associated with higher disease-burden. Despite similar sensitivity, VEP are more associated with clinical variables of disease involvement suggesting that VEP are less affected by false positive values compared with OCT asymmetries. Nevertheless, GCIPL reveals diffuse disease burden in early MS. This was confirmed when correcting for subclinical optic nerve involvement, prompting its role as a marker of global neurodegeneration. Finally, INL thickening does not reveal acute inflammation but a post-acute response to neuronal injury, possibly due to a protective response of Muller cells.