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Category: Investigations
Abstract Title: **Optical coherence tomography detects both neurodegeneration and inflammatory activity in clinically isolated syndromes suggestive of multiple sclerosis.**

Introduction: Neuroretinal changes measured with optical coherence tomography (OCT) can be detected in multiple sclerosis (MS) and in clinically isolated syndromes (CIS) suggestive of MS. Thinning of retinal nerve fibre layer (RNFL) and ganglion cell/inner plexiform layer (GCIPL) reflects neurodegenerative processes, while inner nuclear layer (INL) has been proposed as a marker of inflammation. We aimed at investigating the relationship between OCT measures and other biomarkers, such as cerebrospinal fluid (CSF) oligoclonal bands, microvesicles count (MVs/uL), cytokines and multimodal evoked potentials (mEPs) in CIS.
Methods: We enrolled 111 consecutive patients hospitalized for a first neurological episode suggestive of MS (65% diagnosed with MS according to McDonald 2010 criteria). 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), OCT with peripapillary RNFL and macular GCIPL segmentation. All patients had CSF sampling with oligoclonal bands (OCB) and microvesicles count (MVs/uL) and, in a subgroup (N=30), cytokine dosage (IL1b, IL2, IL4, IL5, IL6, IL7, IL8, IL10, IL12, IL13, IL17, IFNg, MCAF, MIP1b). Only eyes without previous optic neuritis were analysed.
Results: GCIPL and RNFL thickness correlated with visual and global disability: EDSS (r -0.3, p=0.003 and r -0.2, p=0.045 respectively), low contrast VA (r -0.25, p=0.018 and r -0.29, p=0.006). Retinal atrophy was also correlated with mEPs (r -0.3, p=0.003 and r -0.27, p=0.008) MEP and SSEP (respectively r -0.25, p=0.015 and r -0.24, p=0.022), number of T2 lesions (r -0.37, p<0.001 and r -0.38, p<0.001). At multivariate regression brain T2 lesion load and EDSS were the main predictors of RNFL thickness (R=0.47, p<0.001). INL did not correlate with disability measures or with presence of OCB or gadolinium enhancing brain lesions, but with anti-inflammatory cytokines (IL10) and MVs count (r 0.43, p=0.034 and r 0.22, p=0.029 respectively) and inversely associated with the pro-inflammatory MIP1b (r -0.55, p=0.006). IL10 and MIP1b were the main predictors of INL thickness at multivariate regression (R=0.71, p<0.003).
Conclusions: RNFL and GCL are associated with both visual pathway damage (VEP and VA), spinal cord damage (MEP-SSEP, EDSS), and brain lesions and could be considered as indicators of previous structural damage accumulation. Retinal INL thickening is associated with the anti-inflammatory activity following MS relapses, supporting its role as a marker of concurrent immunological activation.