

**Title: Retinal neuro-axonal loss parallels global disability accrual in progressive multiple sclerosis independently from disease activity.**

**Short title: RNFL-GCIPL loss parallels disability in PMS**

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**Background and Aims:** progressive multiple sclerosis (PMS) is a major challenge in neurology. The visual pathway is now as an elective platform to study demyelination and neurodegeneration in MS. We applied functional (visual evoked potentials-VEPs) and structural (optical coherence tomography-OCT) techniques at this level to assess neural damage in PMS.

**Methods:** 350 PMS patients (228 SPMS - 122 PPMS) underwent a cross-sectional evaluation comprehensive of EDSS, visual acuity (VA), full-field (ff-VEPs) as well as multifocal (mf-VEPs) VEPs, and OCT. We obtained follow-up data (mean interval 2.0±0.9 years) for 147 patients (52 PPMS and 95 SPMS) with a parallel collection of clinical records.

**Results:** VEPs latency was higher among SPMS compared to PPMS (mean 144.7 vs 137.4 ms, p=0.001 for ff-VEPs, similar results for mf-VEPs). Retinal Nerve Fiber Layer (RNFL) was thinner among SPMS in comparison to PPMS (mean 79.9 vs 88.5 µm, p<0.001), with similar results for Ganglion Cell-Inner Plexiform Layer (GCIPL), independently from previous optic neuritis (ON). Reclassifying our cohort according to EDSS status (“stability” n.70 vs “worsening” n.53) we found a difference in terms of RNFL evolution (mean annualized percent change -0.2 vs -0.9 %/year respectively, p=0.010), independently from MRI activity, with a correlation between EDSS and RNFL change ( $\rho=-0.359$ , p=0.003).

**Conclusions:** our results suggest a greater functional-structural involvement of the visual system in SPMS compared to PPMS, independently from previous ON. The longitudinal relation between RNFL thinning and EDSS worsening suggests OCT to represent a useful tool to assess disease progression and neuroprotection in PMS.

**Disclosures:** part of this work was supported by Merck, Geneva, Switzerland. Merck is the biopharmaceutical division of Merck KGaA, Darmstadt, Germany.