Progressive multiple sclerosis is associated with accelerated inner and outer retinal layer atrophy

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Background: Optical coherence tomography (OCT) studies have shown that retinal nerve fiber layer (RNFL) and ganglion cell + inner plexiform layer (GCIP) thinning are accelerated in multiple sclerosis (MS). Increased inner nuclear layer (INL) thickness has been associated with inflammatory disease activity, but decreased thicknesses of the INL and outer nuclear layer (ONL) have also been identified in a subset of patients with more severe disability. INL atrophy has also been found post-mortem in MS eyes, more frequently in progressive MS (PMS). These data suggest that there exist differences in retinal pathology at various stages of the disease, however these have been incompletely characterized, as the vast majority of OCT studies comparing retinal measures between MS subtypes have been cross-sectional, with small numbers of PMS eyes.

Objectives: To assess differences in longitudinal changes in retinal layer thicknesses between MS subtypes.

Methods: A single-center cohort of MS patients and healthy controls, followed with serial spectral-domain OCT, was evaluated. Retinal layer thicknesses were derived utilizing a validated, automated segmentation algorithm. Statistical analyses were performed with mixed-effects linear regression models.

Results: Data from 364 MS (178 relapsing-remitting MS [RRMS], 186 PMS) and 66 control participants were analyzed. Median follow-up duration was 3.6 years. Higher age was associated with slower rates of RNFL atrophy in MS ($p<0.001$), but not in controls. Rates of GCIP atrophy did not differ across age in MS, but in controls higher age was associated with accelerated rates of GCIP atrophy ($p=0.006$). The percentage of RNFL and GCIP atrophy in MS attributable to normal aging increased from 42.7% and 16.7% respectively at age 25 years, to 83.7% and 81.1% at age 65 years. PMS was independently associated with accelerated RNFL and GCIP atrophy compared to RRMS (RNFL: $p=0.002$; GCIP: $p=0.001$). Higher age was associated with accelerated INL and ONL atrophy and this relationship was similar in MS and controls. INL and ONL atrophy rates were faster in PMS compared to controls (INL: $p=0.03$; ONL: $p=0.04$) and RRMS (INL: $p=0.008$; ONL: $p=0.01$), but did not differ between RRMS and controls.

Conclusions: PMS is independently associated with accelerated retinal layer atrophy, and INL and ONL atrophy may be novel biomarkers of neurodegeneration in PMS. The effects of normal aging on retinal layer thicknesses should be considered when designing clinical trials incorporating OCT measures as outcomes.