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Abstract Title: **Subclinical neurodegeneration in multiple sclerosis and NMOSD revealed by optical coherence tomography.**

Introduction: Patients affected by multiple sclerosis (MS) show a progressive retinal nerve fiber layer (RNFL) thinning which is correlated to disease activity and cerebral atrophy. It is still unknown if progressive retinal thinning occurs in neuromyelitis optica spectrum disorder (NMOSD).
Methods: Among 68 NMOSD patient referring to the San Raffaele Hospital who had a baseline OCT evaluation, 27 underwent a follow up scan and were enrolled in the study. We used a propensity score based analysis to find a 1:2 matched cohort of MS patients (n=54) with similar baseline characteristics to the NMOSD cohort (age, sex, disease duration, EDSS score, frequency of optic neuritis); also disease activity (presence or absence) during the follow-up was considered in the score. All patients had baseline and follow-up OCT scans and had complete clinical history. In the MS cohort annual or biannual brain MRI scans was available.
Patients were divided according to disease activity: for the MS cohort NEDA3 criteria were used (no relapse, no disability progression, no new or enlarging brain T2 lesions, no gadolinium enhancing brain lesion) while for the NMOSD cohort only clinical criteria were used.
Results: Average follow-up duration was 26.9 months (SD 11.57). We considered mean binocular values of peripapillary RNFL thickness and macular GCIPL thickness; in case of recent optic neuritis (ON within 6 months from baseline) contralateral values were considered, patients with binocular ON were excluded.
A significant reduction between baseline and follow up RNFL thickness was found in 52 active MS (-1.6 um $\pm$ 1.67), 52 MS reaching NEDA (-0.64 um $\pm$ 1.23) and in 20 active NMOSD patients (-1.3 um $\pm$ 1.32) (paired T-test: $p<0.001$; $p=0.033$; $p=0.015$ respectively) while no significant reduction was found in the NMOSD inactive group (n=24, -0.04 um $\pm$ 0.8). Similar findings were found considering GCIPL thickness.
We found that mean binocular RNFL was significantly higher in active rather than in non-active patients in both cohorts (Unpaired T-test: $p=0.002$ for MS and $p<0.001$ for NMOSD) and that MS patients reaching NEDA3 criteria had significantly higher RNFL thinning compared with the non-active NMOSD cohort (Unpaired T-test: $p=0.027$). No significant difference were found among active patients.
We performed a generalized estimating equation analysis with RNFL loss as dependent variable; diagnosis, disease activity, age, gender, disease duration, EDSS, optic neuritis status, MS type (relapsing remitting vs progressive) as independent variables and we confirmed what previously found.
Conclusions: These findings confirm that disease activity is an important determinant of neuroaxonal loss at retinal level both in MS and in NMOSD. We found that NMOSD does not display detectable atrophy rate -at least at retinal level- in absence of clinical relapse. Our data also demonstrate that OCT is able to detect subclinical neurodegenerative processes occurring in MS patients with no clinical or MRI evidences of disease activity.