The title of the doctoral dissertation:

# THE ASSESSMENT OF AXONAL AND NEURONAL DAMAGE IN FAMILIAL AND SPORADIC MULTIPLE SCLEROSIS BY USE OF THE OPTICAL COHERENCE TOMOGRAPHY.

Author: lek. Monika Grudziecka Pyrek, MD

Promotor: Professor Krzysztof Selmaj, MD, PhD

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**Abstract** text:

**Objective**: The assessment of axonal and neuronal damage of retina in patients with familial (fSM) and sporadic (sSM) relapsing – remitting multiple sclerosis.

**Methods:** 45 patients with fMS, 58 patients with sMS and 35 healthy controls were enrolled in the study. The diagnosis of MS in both groups of patients met the 2010 McDonald criteria. In addition, to confirm diagnosis of fMS, these patients needed to have a family member suffering from MS, grade 1 – 3. All participants of the study had OCT examination with the spectral domain optical coherence tomography (SD-OCT, Heidelberg Engineering). OCT images have a high resolution, which allowed for assessment of all layers of the retina, including their thickness and volume. Axonal changes in the retinal nerve fiber layer (RNFL) and neuronal changes in the macula were assessed in patients with sSM and fSM. The mean thickness of the RNFL was analyzed, as well as RNFL thickness in four segments: nasal, inferior, superior, temporal and in the papillomacular bundle (PMB). PMB represents the middle sector of the temporal quadrant. Macular volume (MV) analysis was also performed in the above study groups. Medical history of each participant was obtained and demographic data were collected. The patients were examined neurologically and the degree of disability was assessed using the Expanded Disability Status Scale (EDSS). A comparative analysis of the RNFL thinning and decreasing of the MV was performed

in sMS and fMS. Additionally, the impact of previous optic retrobulbar neuritis (ON) on RNFL and MV was assessed in both fMS and sSM. The correlation between RNFL and MV parameters with gender, neurological disability (measured with EDSS) and duration of MS was also performed.

**Results**: Our study showed a significant thinning of the mean thickness of RNFL in both forms of MS compared to the control group (85.8 (+/- 12.7) μm in fMS, 86.61 (+/- 14.74) μm in sMS, 97.96 (+/- 7.67) μm in the control group; $p < 0.001$). There were no significant differences in the mean RNFL thickness between fMS and sMS (85.8 (+/- 12.7) μm in fMS vs. 86.61 (+/- 14.74) μm in sMS vs.; $p = 0.77$). The analysis of the RNFL thickness in individual segments showed slight differences between both types of MS, with a greater RNFL thinning PMB in fMS than in sMS (41.19 (+/- 10.02) μm vs. 43.98 (+/- 11.1) μm; $p = 0.19$). In the remaining segments, the RNFL thickness was similar in fMS an sSM.

A significant reduction in MV was demonstrated in fMS and sMS patients compared to the control group (8.1 (+/- 1.12) $mm^3$ and 8.12 (+/- 1.14) $mm^3$ vs. 8.81 (+ / - 0.31) $mm^3$; $p = 0.003$), but when comparing MV between fMS and sMS, no differences were found (8.1 (+/- 1.12) $mm^3$ vs. 8.12 (+/- 1.14) $mm^3$; $p = 0.96$).

A significant effect of the previous ON on the parameters of OCT in sMS and fMS was demonstrated. Mean RNFL thickness in the eyes affected by ON was slightly more decreased in sMS than in fMS (78.00 (+/- 10.86) μm vs. 80.86 (+/- 13, 58) μm; $p = 0.37$). When comparing the degree of RNFL thinning in individual segments, a greater reduction was observed in PMB of fMS than in sMS (34.39 (+ / -10.79) μm vs. 38.79 (+/- 7.4) μm; $p = 0.09$). In the remaining segments, RNFL thickness was similar in fMS and sMS. The most significant results were obtained assessing the effect of ON on the macular volume. MV in patients with sMS and previous ON was significantly lower than in the fMS (8.12 (+/- 2.87) $mm^3$ vs. 8.35 (+/- 2.59) $mm^3$; $p = 0.05$).

The analysis of the mean RNFL thickness showed similar values of RNFL in women and men in both forms of MS. In the segmental analysis, a greater reduction in the thickness of RNFL in PMB in fMS was found compared to sMS in women (42.29 (+/- 10.75) μm vs. 45.47 (+/- 10.44) μm; $p = 0.21$), as well as in men (37.77 (+/- 6.59) μm vs. 42.41 (+/- 10.88) μm; $p = 0.21$). Macular volume was similar in men and women in both forms of MS.

Comparing thickness of RNFL and MV in patients with lower disability, <3 EDSS points, no significant differences were found between sMS and fMS. However, in patients with EDSS ≥ 3 in sMS compared to fMS, a greater reduction in the mean RNFL thickness was observed (77.33 (+/- 20.62) μm vs. 83.33 (+/- 11.53) μm; p = 0.37). Also, MV in sMS showed greater reduction than in fMS (8.24 (+/- 0.51) $mm^3$ vs. 8.4 (+/- 0.42) μm in fMS; p = 0.42).

The analysis of the OCT parameters in patients with a shorter MS duration, <10years, showed slightly lower mean RNFL in sMS than in fMS (88,66 +/- (13,75) vs. 91,7 (+/-11,65) μm; p=0,41) and comparable MV (8,53 (+/-0,4)$mm^3$ vs. 8,51(+/-0,44) μm; p = 0,87). In patients with disease duration ≥10 years, an inverse relationship was demonstrated. In these patients, the mean RNFL thickness was lower in fMS than in sMS (82.88 (+/- 9.02) ) μm vs. 85.33 (+/- 14.33) μm; p = 0.5) and MV was slightly lower in sMS than in fMS (8.28 (+/- 0.45) $mm^3$ vs. 8.34 (+/- 0.42) μm; p = 0.65).

**Conclusion:** The obtained results indicate that the thickness of RNFL and the macular volume were similar in both forms of MS and were clearly reduced in comparison to control subjects. These findings confirms the presence of axonal and neuronal damage in sMS and fMS. The main finding of this study is demonstration of differences in RNFL thickness and macular volume between sMS and fMS after retrobulbar optic neuritis. In sMS, neuronal damage, expressed in macular volume measurement, was significantly greater than in the fMS form. Changes in the retina caused by inflammation of the optic nerve, in the classical interpretation, represents a consequence of its demyelination, leading to retrograde axonopathy measured as thinning of RNFL. This pattern of changes was predominantly observed in fMS where thickness of PMB was clearly lower comparing to sMS. However, it has been suggested that MS pathology can also involves primary neuronal damage. Its relationship to inflammation is still under discussion. The significant reduction of macular volume in sMS after ON indicates that such neuronal damage might have occurred in relation to previous optic nerve inflammation in this form of MS. Differences in the degree of axonal and neuronal damage after optic neuritis might indicate a different mechanism of inflammation-induced damage in the retina of familial and sporadic forms of MS.