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Philipp Albrecht
Ruth Fröhlich
Hans-Peter Hartung
Bernd C. Kieseier
Axel Methner

Optical coherence tomography measures axonal loss in multiple sclerosis independently of optic neuritis

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Sirs: Multiple sclerosis (MS), a chronic disabling disorder, is histopathologically characterized by inflammation, demyelination, and axonal loss, the latter being considered as the pathological correlate of clinical disability [2]. Conventional magnetic resonance imaging (MRI) provides insufficient sensitivity and specificity to reveal the degree of damage to the central nervous system. Current evidence is limited to the notion that the commonly used MRI measure of brain atrophy may represent a valuable correlate to ascertain axonal loss in the MS brain [6]. A novel technique, Optical Coherence Tomography (OCT), a non-contact, non-invasive imaging technique based on measuring echo time and scatter of infrared light similar to ultrasound echography, has recently been used to assess axonal loss and damage associated with optic neuritis (ON) [3, 9]. Interestingly, in MS some authors also observed significant reductions of retinal nerve fiber layer thickness (RNFL) even in clinically unaffected fellow eyes [7]. This observation is in line with postmortem studies demonstrating that atrophy of the nerve fiber and ganglion cell layers is present in the majority of MS patients even without a clinical history of ON [4]. Our objective was to use OCT as a technical surrogate in order to demonstrate axonal loss in patients with MS, and to correlate our findings with clinical measures of disability, the clinical subtypes, and a clinical history of ON.

RNFL thickness was assessed by optical coherence tomography using a Stratus OCT Model 3 (Carl Zeiss Meditec AG, Jena, Germany). We performed 3.4 mm diameter circular scans of the optic discs of each eye and used the average RNFL thickness value as a single value corresponding to the whole 360° OCT scan for each eye. We examined 11 control individuals and 24 MS patients (12 relapsing-remitting MS, RRMS, 3 of whom had bilateral and 5 unilateral history of ON; 9 secondary progressive, SPMS, including 3 with bilateral history of ON; 3 primary progressive MS, PPMS, including 2 with bilateral history of ON) who had been diagnosed according to international criteria [8] and clinically evaluated using the Expanded Disability Status Scale (EDSS) [5]. For statistical analysis, we randomly selected one eye of the statistically dependent eyes of control subjects. However, the difference of RNFL thickness between both eyes of MS patients, even without history of ON, was significantly higher than in controls (mean difference in MS patients without ON 14.93 μM ± 4.54 SEM, $n = 11$, mean difference of controls 3.75 μM ± 1.14 SEM, $n = 11$, $P < 0.05$ Mann-Whitney and t-test). We attributed this to subclinical changes independently affecting each eye of the MS patients and therefore considered the eyes of MS patients as statistically independent.

The median RNFL thickness of controls (103.4 μM, SD 10.96, $n = 11$ eyes) was significantly different to that observed in RRMS patients (86.91, SD 21.51, $n = 24$ eyes, $P < 0.05$ ANOVA), SPMS patients (70.57 μM, SD 16.76, $n = 18$, $P < 0.01$ ANOVA) and PPMS patients (80.45 μM, SD 17.76, $n = 6$, $P < 0.05$ ANOVA) (Fig. 1A). Controls were significantly younger than MS patients (34.27 SD 6.21 years vs. 41.82 SD 7.37, $P < 0.01$ Mann-Whitney test) and age affects RNFL thickness [1]. But this cannot account for the differences observed between relapsing-remitting and progressive disease, as these groups did not differ in regard to age (RR-MS 38.75 SD 9.25 years, SPMS 41.78 SD 7.14 and PPMS 43 SD 10) (Fig. 1B). In contrast to previous results, we did not observe a statistically significant difference in RNFL thickness between eyes with and without ON history in our collective of MS-patients (Fig. 1C). However, RNFL thickness correlated significantly to EDSS only in eyes without ON history (no ON $r^2 = 0.175$, $P = 0.05$ Spearman two tailed; ON $r^2 = 0.13$, $P > 0.05$ Spearman), although a trend towards RNFL reduction with increasing EDSS was evident in both groups (Fig. 1D).

We conclude that RNFL thickness as measured by OCT might correlate with a progressive course of disease and with the clinical burden of disease as assessed by EDSS. Axonal loss is a pathological hallmark of progressive MS; we therefore hypothesize that axonal loss measured by OCT also correlates with neuronal degeneration in the brain, which seems to be masked by local changes induced in the optic nerve in the context of ON. Thus, OCT might be a useful

P. Albrecht · R. Fröhlich · H.-P. Hartung · B. C. Kieseier · A. Methner, MD (✉)
Dept. of Neurology
Heinrich Heine Universität Düsseldorf
Moorenstr. 5
40225 Düsseldorf, Germany
Tel.: +49-172/44510481
Fax: +49-40/42803-5101
E-Mail: axel.methner@gmail.com

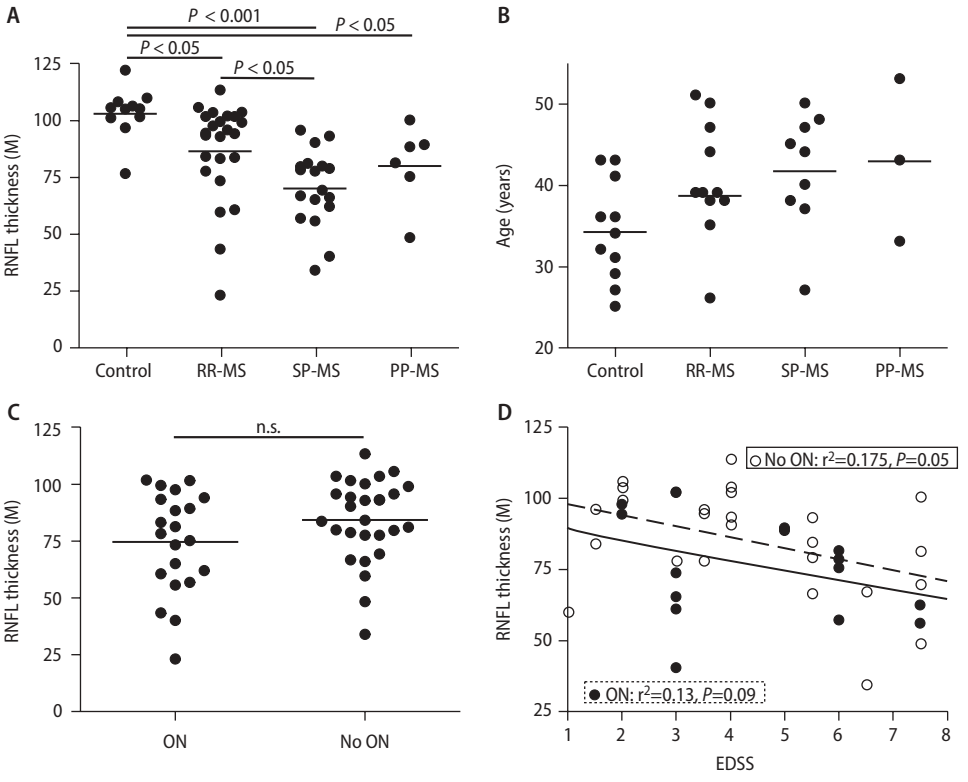

Fig. 1 Dot plot analyses of single eye RNFL thickness (**A**) and age (**B**) in controls, relapsing-remitting (RR-MS), secondary progressive (SP-MS), or primary progressive MS (PP-MS). **C** Dot plot analysis of single eye RNFL thickness with and without history of optic neuritis (ON). **D** Linear regression of RNFL thickness with EDSS scores for patients with (filled circles, continuous line) and without (open circles, dotted line) history of ON. Statistical analysis was done by one-way ANOVA and Dunnet's post-test (**A–C**) or Spearman correlation test (**D**), respectively

surrogate marker to monitor axonal loss and neuronal degeneration in MS. Larger prospective studies are warranted to evaluate the potential of this tool in clinical studies as well as in daily clinical practice.

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