Optical coherence tomography in multiple sclerosis
Thickness of the retinal nerve fiber layer as a potential measure of axonal loss and brain atrophy

Introduction

Multiple sclerosis (MS) is a primary demyelinating disease of the central nervous system with a variable spectrum of clinical and pathological presentation. Although pathologic damage in MS involves the myelin sheath, recent data showed that axonal degeneration might be equally important and occur during early phases of the disease [2]. For assessment of axonal loss in vivo in MS patients several MRI techniques, such as T1 lesion load [21], atrophy measures, and brain parenchymal fraction (BPF) [12], have been applied. All these techniques require advanced technology and extensive examination times.

The retina represents the most proximal part of optic nerve, with a unique structure composed of unmyelinated axons and with some contribution from glial cells [8, 13]. This axonal distribution creates a retinal nerve fiber layer (RNFL) and its thickness correlates with changes in axonal function [4]. A reduction in the RNFL has been observed in patients with several optic neuropathies [1]. Qualitative changes in RNFL in MS patients was first reported by Frisen and Hoyt [7]. Quantitative changes in RNFL in optic neuritis were first described by Parisi et al. [14], Trip et al. [19] and Fisher...
et al [6]. Recently published data have also shown a reduction of RNFL in patients with optic neuritis, one of the primary clinical presentations of MS in MS patients without a history of optic neuritis [17]. Although there are a few methods for retinal imaging, including Scanning Laser Polarimetry (GDx with variable corneal compensation) and Confocal Scanning Laser Ophthalmoscopy (Heidelberg retinal tomography), results from several studies have suggested that OCT is the best method for assessment RNFL in MS [8]. This is a non-invasive diagnostic technique, based on echo time delay of back-scattered infrared light, that is used in ophthalmology to investigate the retina and optic nerve [3]. Thus, the application of OCT for the assessment of MS patients is a reliable method that can be used for the direct quantification of axonal loss in the optic nerve.

The goal of this study was to estimate whether RNFL as measured by OCT may represent a new structural parameter in the evaluation of global axonal loss in MS patients. We hypothesized that axonal loss in RNFL would correlate with brain axonal damage and that RNFL would correlate with neurological impairment and disease duration in MS. In essence we searched for a correlation between OCT measurements of RNFL and brain tissue damage as assessed by MRI.

Methods

Subjects

We included 51 patients with a diagnosis of relapsing-remitting MS (RR-MS) based on McDonald criteria [15] in the study. None of these patients had been treated with immunomodulatory or immunosuppressive drugs. We divided our patient population into two subgroups: MS with optic neuritis (MS ON) in the past and without optic neuritis (MS N-ON). Most of our MS-ON patients had a single attack of unilateral ON and four have subsequent optic neuritis in both eyes. In the MS ON group we compared OCT measures between the affected eye (AE) and the unaffected eye (UA). Age- and sex-matched healthy control subjects (HC), with no history of neurological and ocular disease and unrelated to the MS participants, were included in the study as a control group. We excluded from analysis subjects with high myopia. The neurological status of all MS patients was determined and included the Expanded Disability Status Scale (EDSS) [10]. The study was approved by the local ethics committee.

Magnetic resonance imaging

MRI scans were obtained on a 1.5 Tesla scanner (Vision Plus, Siemens, Erlangen, Germany). The MRI protocol included dual-echo (TR = 5000 ms, TE = 20/80 ms; 50 slices, thickness = 3 mm; gap = 0.0 mm, matrix 154 x 256, and FOV = 250 x 250 mm), T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE – TR = 9.7 ms, TE = 4 ms; eff thick 1.5 mm, no partitions 164, matrix 192 x 256).

MRI data analysis included assessment of total lesion volume on T2- and T1-weighted images using semi-automated techniques (Java Image, Xipanse, UK). Brain atrophy was measured using T1-3D MPRAGE and SMP 99 software (Wellcome Department of Cognitive Neurology, University College of London, UK). White matter (%wm), gray matter (%gm) fraction and brain parenchyma fraction (BPF) were calculated according to an accepted formula [5].

Optical coherence tomography

After mydriasis of both eyes with 1 % tropicamide, the fast RNFL protocol included three 3.4 mm diameter scans, with samples of 256 points. The OCT 4.0 software (Stratus version 3, Carl Zeiss Meditec Inc, Dublin, CA) was used. For analysis only scans with a signal strength ≥ 7 and uniform brightness across the scan circumference were used. The average and quadrants (temporal, superior, nasal and inferior) RNFL were measured.

Statistical analyses

Statistical analyses were performed with SPSS (version 14.0) package. The normal distribution of all variables was tested using the Kolmogorov-Smirnov test. Using the t-test we compared EDSS and disease duration between two group of MS patients. Spearman’s rank test was used to assess correlation between EDSS and RNFL and Pearson’s correlation was applied to examine correlations between RNFL and MRI data. We used mean value of RNFL of both control eyes to analyze the data. All statistical tests were regarded as significant at p < 0.05.

Results

The clinical characteristics of the MS patients and control groups are shown in Table 1 and confirm appropriate matching in relation to age, EDSS and disease duration (p > 0.05).

RFNL in patients with optic neuritis

The average RNFL in the AE was lower compared with the UE (83.92 ± 17.63 versus 91.08 ± 19.3). Accordingly, RNFL in the AE of MS ON patients was significantly lower compared to the average RNFL in MS N-ON patients (83.92 ± 17.63 versus 94.38 ± 15.0, p = 0.01) and in HC (83.92 ± 17.63 versus 100.3 ± 12.1, p = 0.01) (Table 2). In addition, RNFL of the UE in MS ON patients was also reduced, albeit not significantly, compared with average RNFL in MS N-ON patients (91.08 ± 19.3 versus 94.38 ± 15.0) and with HC (91.08 ± 19.3 versus 100.3 ± 12.1). Sectoral analysis showed that, compared with MS N-ON, RNFL thickness in the AE was significantly lower in the

Table 1  Clinical characteristic of MS patients and HC

<table>
<thead>
<tr>
<th></th>
<th>MS ON (n = 20)</th>
<th>MS N-ON (n = 31)</th>
<th>HC (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>33 (6.6)</td>
<td>34 (4.6)</td>
<td>31 (3.3)</td>
</tr>
<tr>
<td>EDSS, median (SD)</td>
<td>2.49 (1.03)</td>
<td>2.40 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>7.1 (2.2)</td>
<td>6.9 (3.2)</td>
<td></td>
</tr>
</tbody>
</table>

SD standard deviation; y year