Short report

Retinal inter-eye difference and atrophy progression in multiple sclerosis diagnostics

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ABSTRACT

Background The visual system could be included in the diagnostic criteria for multiple sclerosis (MS) to demonstrate dissemination in space (DIS) and dissemination in time (DIT). Objective To investigate the diagnostic value of retinal asymmetry in MS. Methods A prospective, longitudinal study in individuals with MS (n=151) and healthy controls (n=27). Optical coherence tomography (OCT) was performed at 0, 2 and 4 years. Macular ganglion cell and inner plexiform layer (mGCIPL) thickness was determined as well as measures for retinal asymmetry: the inter-eye percentage difference (IEPD) and inter-eye absolute difference (IEAD). Receiver operator characteristics curves were plotted and the area under the curve (AUC) was calculated for group comparisons of the mGCIPL, IEPD, IEAD and atrophy rates. Results The diagnostic accuracy of both the IEPD and IEAD for differentiating bilateral and unilateral MS optic neuritis was high and stable over time (AUCs 0.88–0.93). The IEPD slightly outperformed the IEAD. Atrophy rates showed low discriminatory abilities for differentiating MS from controls (AUC 0.49–0.58). Conclusion The inter-eye differences of the mGCIPL have value for demonstration of DIS but in individuals with longstanding MS not for DIT. This may be considered as a test to detect DIS in future diagnostic criteria. Validation in a large prospective study in people presenting with symptoms suggestive of MS is required.

INTRODUCTION

The potential role for retinal optical coherence tomography (OCT) for diagnostic criteria for multiple sclerosis (MS) had been identified.1 The contribution of a paraclinical test to the diagnostic criteria has evolved to permit for substitution for dissemination in space (DIS) and dissemination in time (DIT) of MS disease pathology.2–5 There is mounting evidence that OCT permits for highly sensitive, accurate and reproducible detection of retinal atrophy as a result of optic neuritis.6–7 Recently, a simple measure for retinal asymmetry has been identified.6–14 This measure gives a single numeric value. The inter-eye difference (IED) is calculated from the inner retinal layer thicknesses of the right and left eye. The IED can be expressed as a dimensionless percentage value (IEPD) or as an absolute value (IEAD) in µm. Several studies have now provided evidence that these measures for retinal asymmetry permit to reliably identify a previous episode of MS-associated optic neuritis (MSON). The diagnostic accuracy is high in differentiating these patients from healthy controls and from patients without a previous episode of MSON (non-MSON).12,13 This suggests that the OCT may qualify as a useful assessment tool to detect a fifth central nervous system location for DIS.12,14 To date retinal asymmetry has only ever been applied in cross-sectional data sets. It is not known how well measures of retinal asymmetry perform over time. As a potential diagnostic test for MS it is relevant to note that these measures of retinal asymmetry also identify individuals with MS who never had MSON according to the contemporary definition.5,9 It is understood that MS lesions affecting the posterior visual pathway trigger retrograde trans-synaptic axonal degeneration which reaches the retina, thereby causing retinal asymmetry.15–17 While encouraging, these findings only encourage a role of OCT as a substitute for DIS in MS diagnostics. The value of OCT for potential substitution for DIT is not known. Therefore the present prospective longitudinal study investigated the diagnostic value of retinal asymmetry for DIS and DIT.

METHODS

Written informed consent was obtained from all subjects before study inclusion.

Study design and participants

For this prospective study, patients suffering from MS and healthy control (HC) subjects were enrolled from the Amsterdam UMC. All subjects underwent clinical and OCT assessments at baseline, 2 years and 4 years. The diagnosis of MS and MSON was made according to consensus criteria.3,18 This consisted of a detailed history-taking (pain worsening on eye movements, timing of visual loss and patterns of recovery) and review of medical records. Patients were subdivided into relapsing–remitting, secondary progressive and primary progressive MS.19 Clinical assessments included physical and cognitive disability scales and visual function as reported before for this cohort.12,20,21

Optical coherence tomography

Spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was performed and OCT quality assessment was based on validated consensus criteria, as previously described.22–24 The thickness of the macular ganglion cell and inner plexiform layer (mGCIPL) and parapapillary nerve fibre layer was determined. The inter-eye differences of the mGCIPL were calculated as...
described previously. For each analysis we used both the inter-eye percentage difference (IEPD, a dimensionless metric) and inter-eye absolute difference (IEAD, in μm) from the ETDRS grid. The atrophy rates were calculated by dividing the GCIPL difference between two time points by the follow-up time in years (annualised atrophy rates).

Statistical analysis
Analyses followed EQUATOR (Enhancing the QUAlity and Transparency Of Health Research) reporting guidelines and were consistent with the Strengthening the Reporting of Observational Studies in Epidemiology outline for cohort studies. SAS V9.4m7 (SAS Institute) was used for all analyses. Data distribution was checked by the Shapiro-Wilk test and visually. Normally distributed data were presented as mean and SD. The median and IQR were shown for non-Gaussian data. Categorical data were presented as number (percentage). Statistical analyses of the OCT data and reporting followed consensus guidelines. The accuracy of diagnostic performance was tested using receiver operator characteristics (ROC) curve analyses. Areas under the curve (AUC) and 95% CI for the ROC curves are visualised in online supplemental figure 1.

RESULTS
In total 151 patients with MS and 27 HCs were included. The demographic and clinical characteristic are summarised in table 1. Patients had a mean disease duration of 20.8 (±6.5) years and 98 (65.5%) showed a relapsing–remitting disease course. Eighty patients (53%) had experienced a clinically identified episode of MSON, of which 30 bilaterally. Characteristic of the MSON groups are shown in table 1.

### Table 1 Subject characteristics (baseline)

<table>
<thead>
<tr>
<th>Patients with MS</th>
<th>All (n=151)</th>
<th>Non-MSON (n=71)</th>
<th>Unilateral MSON (n=50)</th>
<th>Bilateral MSON (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (N, female)</td>
<td>12 (44)</td>
<td>45 (63)</td>
<td>34 (68)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.2±5.4</td>
<td>56.1±9.0</td>
<td>51.3±9.2</td>
<td>52.2±10.6</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>N/A</td>
<td>20.3±6.5</td>
<td>20.4±6.5</td>
<td>22.9±6.1</td>
</tr>
<tr>
<td>EDSS score</td>
<td>3.5 (3.0–5.0)</td>
<td>3.5 (3.0–6.0)</td>
<td>3.5 (2.5–5.0)</td>
<td>4.0 (3.0–4.5)</td>
</tr>
<tr>
<td>Disease course</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Relapsing–remitting (N)</td>
<td>N/A</td>
<td>42 (59)</td>
<td>36 (72)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Secondary progressive (N)</td>
<td>N/A</td>
<td>11 (32)</td>
<td>14 (28)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Primary progressive (N)</td>
<td>N/A</td>
<td>18 (25)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Current DMT use (N)</td>
<td>N/A</td>
<td>16 (23)</td>
<td>19 (38)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>mGCIPL mean ODS (μm)*</td>
<td>92.1±6.2</td>
<td>82.6±12.6</td>
<td>72.8±12.4</td>
<td>70.7±15.4</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD, median (IQR) or N (%). *Baseline GCIPL ODS values available for 24 healthy controls and 118 patients with MS.

Disease modifying treatment; EDSS, Expanded Disability Status Scale; mGCIPL, macular ganglion cell and inner plexiform layer; MS, multiple sclerosis; MSON, multiple sclerosis-associated optic neuritis; N, number; N/A, not applicable; ODS, left and right eye.
found when a group of patients with unilateral optic neuritis (not specifically due to MS) was compared with HCs. When the reference is a diseased group, sensitivity and specificity drop, to respectively 67.3% and 67.4% when comparing MSON to non-MSON. Our longitudinal result confirms the previous cross-sectional finding that the inter-eye differences also have a high diagnostic accuracy for bilateral MSON, besides for unilateral MSON.

In our study and previous studies, the diagnostic accuracy was higher for the IEPD than the IEAD. One advantage of the IEPD is that it is a dimensionless measure, with might be helpful for pooling data from different devices and different segmentation software. This however has to be confirmed in future studies which investigate different devices in parallel. The IEPD is probably not sensitive in differentiating MSON from other types of optic neuritis. Therefore it could be useful as an additional paraclinical test in the diagnosis of MS.

The diagnostic accuracy of the inter-eye differences for differentiating non-MSON from HCs was moderate to good (AUC 0.66–0.73). The 5% cut-off for the IEPD resulted in sensitivity values between 41% and 49%. This suggests that at least part of this group has either suffered from a subclinical optic neuritis or asymmetrical pathology further along the visual pathway, resulting in retrograde (trans-synaptic) degeneration. A limitation of the present study is that we cannot make conclusion about the aetiology of this asymmetry. Studies in earlier phases of the disease with frequent radiological and OCT follow-up would be useful in evaluating the chain of events leading to (asymmetrical) retinal atrophy. Future development of automated region of interest analysis are eagerly awaited as they permit for a more detailed comparison of hemispheric asymmetry in MS lesion distribution. Presently this is still a very labour and time consuming manual approach.

The atrophy rate of the mGCIPL was similar in our MS group and the HC group. One reason for this could be the relatively long disease duration of the patients with MS. Previous studies have shown that thinning of the retinal layers occurs most rapidly during the early stages of diseases. Potentially, in the larger part of our group a plateau effect occurred, which is a limitation of the present study. Extending the current approach to a MS group early in the disease could be useful. Related to this, the target population for using inter-eye differences for DIS would be patients suspected of (relapsing–remitting) MS. This differs from our population with a longer disease duration and more frequently a progressive disease type. Another limitation of our study is that we cannot make conclusion about the aetiology of this asymmetry. Studies in earlier phases of the disease with frequent radiological and OCT follow-up would be useful in evaluating the chain of events leading to (asymmetrical) retinal atrophy. Future development of automated region of interest analysis are eagerly awaited as they permit for a more detailed comparison of hemispheric asymmetry in MS lesion distribution. Presently this is still a very labour and time consuming manual approach.

In conclusion, the inter-eye percentage differences (IEPD) and the inter-eye absolute difference (IEAD) at baseline, year 2 and year 4. The red line indicates the 5% cut-off for the IEPD and the 4 μm cut-off of the IEAD. BON, bilateral MS associated optic neuritis; HC, healthy controls; MS, multiple sclerosis; NON, no MS associated optic neuritis; ON, unilateral MS associated optic neuritis. The median (bold horizontal line), 25–75 percentiles (box), 5–95 percentiles (whiskers), mean (symbol in the box) and outliers (symbols outside the box) are shown.

DISCUSSION

The main finding of this study was that the inter-eye difference of the mGCIPL has a high accuracy in diagnosing patients with MS with both unilateral and bilateral optic neuritis over time. The IEPD showed a slightly higher accuracy than the IEAD. The atrophy rate of mGCIPL over a 4-year period showed a low discriminatory value for differentiating patients with MS from HCs in this group of patients with longstanding disease.

Our results on the diagnostic accuracy of inter-eye differences are in line with previous literature. In online supplemental table 3, sensitivity and specificity of optimised cut-off of the inter-eye differences of the mGCIPL in these studies are summarised. Both diagnostic accuracy and the optimised cut-off value varied depending on the groups compared in the study. Highest accuracy (sensitivity 100% and specificity 98%) was relevant diagnostic cut-off for the atrophy rate could be determined. Similar to the atrophy rate, the IEPD and IEAD did not substantially change over time, both for patients with MS and HCs (online supplemental figure 2 B+C, and online supplemental figures 5 and 6 for individual subjects).

Contributors JNB - Data analysis and interpretation, writing & revision of manuscript BMJU - Data interpretation, critique & revision of manuscript AP - Data analysis and interpretation, writing & revision of manuscript

Figure 1 Box-and-Whisker plots of (A) the inter-eye percentage differences (IEPD) and (B) the inter-eye absolute difference (IEAD) at baseline, year 2 and year 4. The red line indicates the 5% cut-off for the IEPD and the 4 μm cut-off of the IEAD. BON, bilateral MS associated optic neuritis; HC, healthy controls; MS, multiple sclerosis; NON, no MS associated optic neuritis; ON, unilateral MS associated optic neuritis. The median (bold horizontal line), 25–75 percentiles (box), 5–95 percentiles (whiskers), mean (symbol in the box) and outliers (symbols outside the box) are shown.
Multiple sclerosis

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