Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis

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Optical coherence tomography (OCT) is a new method that could aid analysis of neurodegeneration in multiple sclerosis (MS) by capturing thinning of the retinal nerve fibre layer (RNFL). Meta-analyses of data for time domain OCT show RNFL thinning of 20·38 μm (95% CI 17·91–22·86, n=2063, p<0·0001) after optic neuritis in MS, and of 7·08 μm (5·52–8·65, n=3154, p<0·0001) in MS without optic neuritis. The estimated RNFL thinning in patients with MS is greater than the extent expected in normal ageing, probably because of retrograde trans-synaptic degeneration and progressive loss of retinal ganglion cells, in addition to the more pronounced thinning caused by optic neuritis if present. RNFL thickness correlates with visual and neurological functioning as well as with paraclinical data. Developments that could improve understanding of the relation between structure and function in MS pathophysiology include spectral or Fourier domain OCT technology, polarisation-sensitive OCT, fluorescence labelling, structural assessment of action-potential propagation, and segmentation algorithms allowing quantitative assessment of retinal layers.

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Introduction

Optical coherence tomography (OCT) is a non-invasive technique[1] that enables a so-called optical biopsy of accessible tissues such as the retina (figure 1). During the past decade, OCT has matured into an interesting and highly sensitive method for imaging of neurodegeneration in multiple sclerosis (MS);[2,3] because the retina is the only place where a tissue layer made up of axons can be imaged directly, quantification of the retinal nerve fibre layer (RNFL) has the potential to open a diagnostic window for monitoring of neurodegeneration. Loss of visual function is a frequent presenting sign in MS and can be caused by optic neuritis (MSON). Most patients with MSON have good recovery of visual function, but demyelination, ion-channel redistribution, and axonal loss cause remaining subtle signs and symptoms. Visual function is affected in most patients with longstanding MS, and loss of vision is the second most important deficit causing reduced quality of life. Because axonal loss, by contrast with demyelination, is not reversible and is therefore an important cause of sustained disability, a validated tool for monitoring of axonal loss is needed.

We present a systematic review of studies investigating OCT in patients with MS. Special care is taken to distinguish axonal damage caused by clinically evident MSON from more subtle retinal axonal damage in unaffected eyes of patients with MS. We review the anatomical and functional correlations, focusing first on the visual system and second on more global measures of disability in MS. The relation between OCT data and established electrophysiological techniques and imaging modalities is also discussed. Finally, we provide a glimpse into future research areas of advanced OCT imaging that might affect assessment of axonal damage relevant to a patient's disease activity and response to treatment.

Methods

Search strategy and selection criteria

We searched Dutch, English, French, German, Italian, and Spanish literature for all studies using OCT in patients with MS from the first description of the method by Huang[1] in 1991, to May, 2010, including reports published online ahead of print. We searched PubMed, Embase, Medline, Web of Science, and the Cochrane Register of Diagnostic Test Accuracy Studies using the search terms: "multiple sclerosis", "MS", "optic neuritis", "ON", "optical coherence tomography", "OCT", "retinal nerve fibre layer", and "RNFL". Of 96 studies identified, 62 were excluded because they were reviews, did not use the Stratus OCT, were single case reports, communications in response to an article, or duplication of data already published for the cohort, or because data presentation was not detailed enough to allow inclusion in a meta-analysis. Studies that did not include a control cohort were included only if they compared the MSON-affected and unaffected eyes in patients with MS. Of the 34 included studies, 32 presented data suitable for meta-analysis of RNFL thickness between groups.[4–37]

Statistical analysis

We used the Cochrane Collaboration's Review Manager software (RevMan5) for data analysis, following the guidance of the Diagnostic Test Accuracy Working Group. Published data for RNFL thickness were entered as a continuous variable. We used inverse variance with random effects in the model. For effect measure we chose the mean difference, which allows comparison of RNFL thickness (μm) between the groups of interest. We undertook three group comparisons for RNFL thickness: (1) MSON-affected eyes versus the eyes of healthy controls; (2) eyes of patients with MS without history of optic neuritis versus the eyes of healthy controls; and (3) within patients with MS, the MSON-affected eye versus the unaffected eye. Regression analyses were done with SAS software (version 9.1.3). A p value of 0·05 or less was regarded as significant.

OCT in MS

Axonal loss in the retina

With the invention of the ophthalmoscope by von Helmholtz in 1851, in-vivo detection of optic-disc atrophy

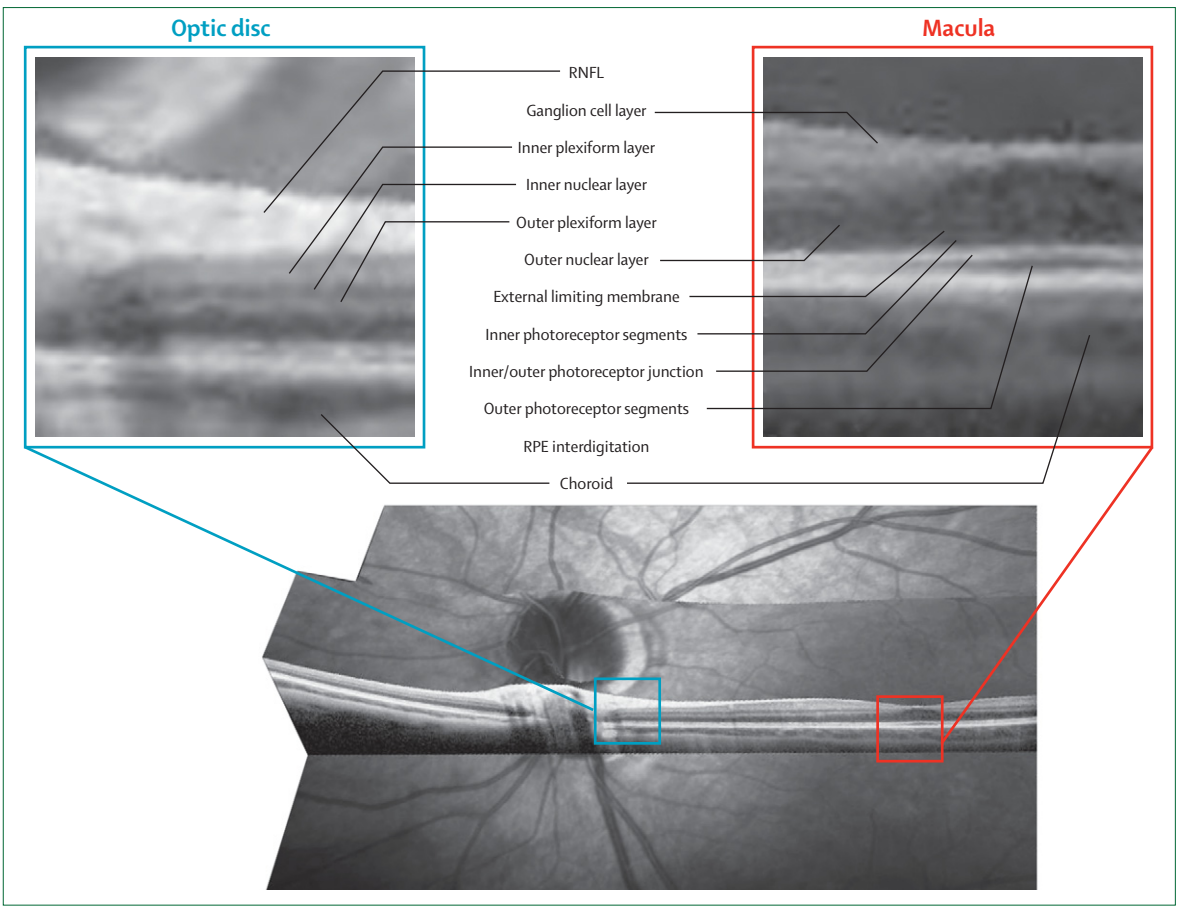

Figure 1: **Spectral or Fourier domain OCT image of a normal eye showing retinal layers**
Inlays show enlarged parts of the optic disc and macula. OCT=optical coherence tomography. RNFL=retinal nerve fibre layer. RPE=retinal pigmented epithelium.

became technically possible. For example, in 1879, Gowers[38] described sectoral RNFL loss in a woman with syphilis. In this case, the remaining nerve fibres were more visible than normal because of swelling.[38] A later case of sectoral RNFL loss in which sequential in-vivo images allowed identification of ascending axonal degeneration (now known as Wallerian degeneration) was facilitated by the rare presence of myelinated fibres in the retina.[39] In 1921, Bachmann described a 28-year-old man in whom sudden loss of vision in the right eye was due to a central retinal artery occlusion.[39] Within 2 months after the retinal vascular event, RNFL loss became visible as degeneration of bundles of myelinated retinal axons (figure 2A), progressing during the next 2 months (figure 2B), and leading to complete optic atrophy and loss of myelinated axons observed on fundus examination within a year (figure 2C).[39] In addition to these early studies, recent work has provided good post-mortem evidence for RNFL thinning in MS.[40]

RNFL in MSON

In MSON, loss of RNFL thickness is in the range of 5–40 µm, averaging at 10–20 µm.[6] This loss was significant in all studies using time domain OCT (TD-OCT) technology based on the Stratus OCT (Zeiss, software version 3.0 and 4.0) that we identified in a systematic literature review. Figure 3 shows summary data for 14 studies of patients with MSON,[4,10,11,15,17,18,20–25,29,37] containing a total of 2063 eyes tested with OCT. Published data from two of these studies were not in a format allowing inclusion into the meta-analysis, and more detailed information could not be obtained from the researchers.[18,22] The results of the meta-analysis of the remaining 12 studies,[4,10,11,15,17,20,21,23–25,29,37] comparing MSON-affected eyes with the eyes of healthy controls, were highly significant, with an estimated average RNFL loss after MSON of –20·38 µm (95% CI –22·86 to –17·91).

An important limitation of these studies is that optic-nerve damage, independent of whether this damage occurs in the context of MSON or due to other causes,[41] will cause some RNFL loss. In a small case series, Choi and colleagues[42] presented detailed OCT data for patients with several kinds of optic neuropathy. Any form of optic-nerve damage was associated with thinning of the RNFL. Therefore, the question arises as to whether the presence of MSON could have introduced a bias into the studies

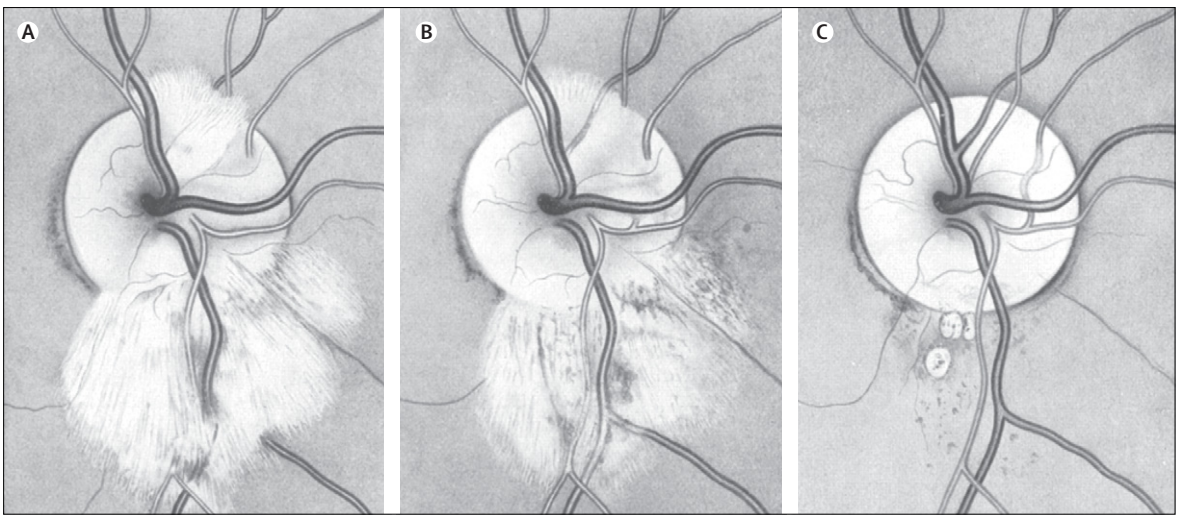

Figure 2: **Hand-sketched illustrations of development of axonal degeneration in the retina, 1921**
At the time, this observation was possible only because of two anatomical oddities coinciding in a 28-year-old man with mitral valve insufficiency: first, the presence of myelinated axons within the retina (a developmental occurrence), seen here as a small white bundle at the top and large white bundle at the bottom of the optic disc; second, occurrence of a central retinal artery occlusion in the same patient, which caused retinal axon degeneration over time. (A) A few dark gaps are visible between the inferior bundle of myelinated axons (sketch made 2 months after sudden loss of vision in the right eye), showing the beginning of loss of axons and their myelination. (B) Axonal loss becomes more apparent after 4 months, and (C) complete optic atrophy is the end result a year after a presumed embolus of the central retinal artery. Bachmann speculated that the mechanism leading to this fundus appearance could have been ascending (Wallerian) axonal degeneration. Note that the very occasional presence of myelinated retinal axons, as seen in this sketch, will affect RNFL data acquired by OCT, because intraretinal myelination results in a thicker, more highly reflective RNFL in those areas. MS patients with myelinated retinal axons can appear as normal or above normal outliers in treatment trials using OCT as an outcome measure, especially if the myelinated retinal axons are undamaged initially. Reproduced from reference 39, by permission of Springer. RNFL=retinal nerve fibre layer. OCT=optical coherence tomography. MS=multiple sclerosis.

shown in figure 3 towards more damage and RNFL thinning than would be expected from MS alone.

In the absence of MSON, retrograde trans-synaptic retinal ganglion cell (RGC) degeneration due to MS lesions within the posterior optic pathways could cause RNFL loss. The existence of retrograde trans-synaptic degeneration of RGCs has been shown in patients with stroke affecting the posterior visual pathways and cortex.[43,44] In a combined MRI and OCT study, Reich and co-workers[45] showed that damage to the optic radiations in MS was associated with a reduced average global RNFL thickness. There is a need to investigate whether the effect of postgeniculate lesions[43,44] on the RNFL can be distinguished from RNFL loss caused by subclinical damage to the anterior visual pathways in MS, as suggested by visual evoked potential (VEP) studies.[46–50]

RNFL in MS without optic neuritis

We identified 16 studies comparing RNFL thickness in patients with MS who did not have evidence of optic neuritis with a healthy control population,[4,10,11,13–15,18–21,23–26,29,37] of which 15 studies provided data in a format allowing inclusion in the meta-analysis.[4,10,11,13–15,19–21,23–26,29,37] Figure 4 shows the summary data for the 3154 eyes investigated. The estimated RNFL loss in MS compared with controls (–7·08 μm) was less than after MSON (–20·38 μm), but the 95% CI was smaller (–8·65 to –5·52). This finding emphasises the importance of looking carefully for evidence of MSON to reduce the risk that detection of more subtle RNFL loss due to presumed retrograde trans-synaptic RGC degeneration could be masked by the pronounced loss caused by damage to the anterior visual pathways in MSON.

RNFL in MS: MSON-affected eye versus contralateral eye

27 studies compared the affected (MSON) eye to the clinically unaffected eye in patients with MS.[4–12,15,16,20–23,25,27–37] The meta-analysis of the 4199 eyes investigated clearly illustrates the significant effect that presence of MSON has on the RNFL (figure 5). The estimated RNFL loss (–14·57 μm, 95% CI –16·50 to –12·63) in MSON-affected eyes versus unaffected eyes is larger than that calculated for the comparison of MS without optic neuritis and controls (–7·08 μm). An important prognostic finding of these studies was that above a threshold of about 75 μm loss of RNFL thickness, the chances of recovery of visual function seem to be reduced.[6]

Conclusion

Taken together, the published data[4–37] suggest an association between RNFL thinning and MS pathology, as shown in figure 6. The retinal axons project through the optic nerve into the lateral geniculate nucleus (LGN). About 90% of retinal axons synapse in the LGN and travel with the optic radiations to the occipital cortex. The remaining 10% project into the pretectal region of the midbrain. Severe thinning of the RNFL follows MSON directly (figure 6B). These acute changes in patients with MSON can be distinguished from chronic changes

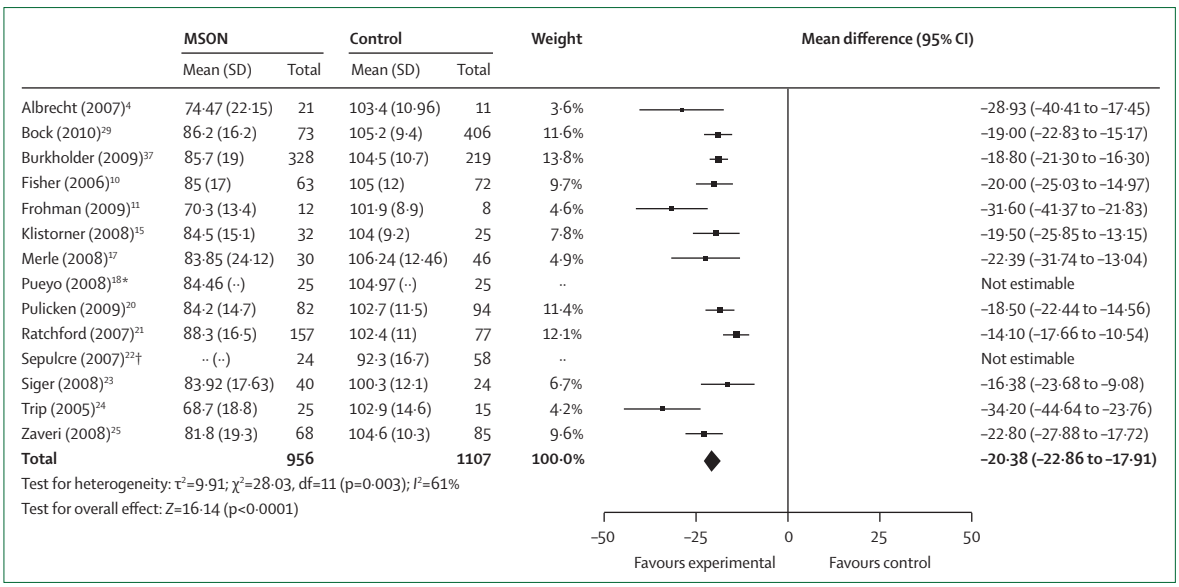

Figure 3: **Meta-analysis of OCT studies in patients with MSON**
Overall averaged RNFL thickness and number of eyes investigated is shown for patients and controls. Mean difference in RNFL thickness between eyes with optic neuritis and normal eyes is shown in µm. OCT=optical coherence tomography. MSON=multiple sclerosis optic neuritis. RNFL=retinal nerve fibre layer. *SD not available from author. †Data (mean, SD) for eyes with optic neuritis were not published and were not available from investigators.

caused by MS pathology of the optic pathways. An MS lesion affecting fibres in the optic radiation will cause Wallerian degeneration (ie, anterograde degeneration) of some axons, which reaches the LGN only after some time. Because of trans-synaptic degeneration, retrograde axonal degeneration will eventually cause some RNFL thinning (figure 6C). Progressive loss of RGCs is also likely to occur in patients with MS as a result of chronic changes in the optic nerves or anterior visual pathways themselves (figure 6D). To test this hypothesis, we reviewed the literature for the timecourse of RNFL loss in patients with MS with and without optic neuritis.

Timecourse of RNFL loss in MS

As a rule of thumb, RNFL loss becomes readily detectable with OCT about 3 months after acute optic neuritis. Early reduction in RNFL thickness caused by axonal atrophy is clinically difficult to distinguish from a reduction due to resolution of axonal swelling, which is common in acute optic neuritis. Costello and colleagues[7] presented longitudinal data for RNFL thickness during the first 12 months after optic neuritis (figure 7). These data show continuing axonal loss in the affected eye for at least 12 months, but most thinning occurs by 6 months after injury.

An inverse correlation between disease duration and average overall RNFL thickness was shown by some investigators (r=–0·262, p=0·011;[18] r=–0·6, p=0·02;[23] p=0·03, r value not published[10]), but not by others.[14,15] Examining eyes not affected by MSON, Henderson and colleagues[14] showed that the RNFL decreased by 0·12 µm per year of disease (95% CI –0·50 to 0·25), but this finding was not significant (p=0·513). Investigating eyes with MSON, Klistorner and co-workers[15] did not identify a correlation between RNFL thickness and disease duration (p=0·9, r value not published). The divergent results[10,14,15,18,23] might in part be accounted for by variation in average disease duration and a bias in the population of patients with MS studied. A meta-regression analysis of the studies' raw data might help to shed light on the presumed association between RNFL loss and disease duration, but the most accurate information will come from longitudinal studies, in which RNFL thickness in individual patients can be studied over time. Talman and colleagues[36] published longitudinal data for 593 eyes that were assessed at baseline and 6 or more months later. Their statistical analysis was corrected for patients' age and adjusted for within-patient and inter-eye correlations. For MSON eyes, the decrease in RNFL thickness compared with baseline was 0·4% (0·4 µm, 95% CI 1·16 to –0·35) for eyes with a 0·5–1 year follow-up; 1·7% (1·6 µm; 2·47 to 0·70) for 1–2 years; 3·2% (2·9 µm; 4·02 to 1·86) for 2–3 years; and 6·7% (6·1 µm; 7·73 to 4·41) for more than 3 years of follow-up. By contrast, the average RNFL thinning for disease-free control eyes was 0·5% (0·49 µm; 1·36 to –0·39) during a 3-year period.[36] Their pooled analysis (MSON-affected and unaffected eyes) showed that each year of follow-up was associated with an average 2 µm increase in RNFL thinning (p<0·001, generalised estimating equation models).[36]

One needs to be very careful when drawing conclusions about the timecourse of RNFL loss in an individual eye from cross-sectional data. The data suggest that in MS without optic neuritis the estimated yearly thinning of the overall RNFL (roughly 2 µm[36]) is probably below the

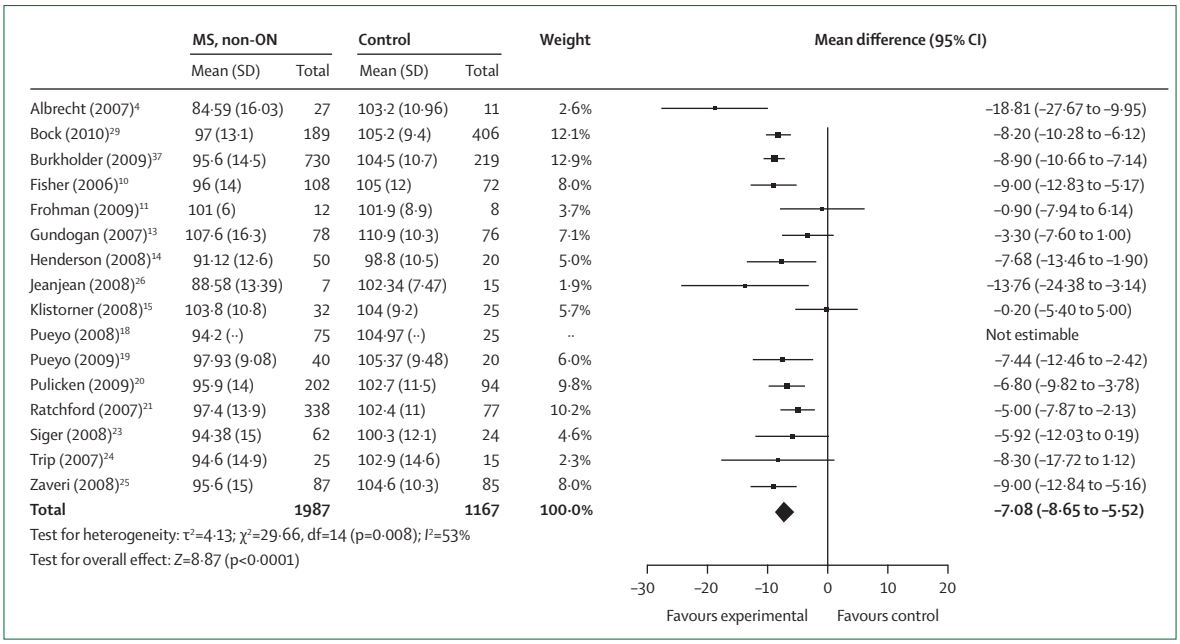

Figure 4: **Meta-analysis of OCT studies in patients with MS without ON**
Overall averaged RNFL thickness and number of eyes investigated is shown for patients and controls. Note that the plotted data, summarising the difference in RNFL thickness between asymptomatic eyes and control eyes, show that there is loss of RNFL even in eyes without previous optic neuritis. OCT=optical coherence tomography. MS=multiple sclerosis. ON=optic neuritis. RNFL=retinal nerve fibre layer. *SD not available from author.

detection limit of TD-OCT systems. Theoretically, the new spectral or Fourier domain OCT (SD/FD-OCT) systems should enable resolution at this level,[51–54] but, practically, a resolution of 4–6 μm was shown for the Heidelberg spectralis and Cirrus HD-OCT.[55] There was no quantifiable RNFL loss in patients with a recent-onset (average of 4·3 months) clinically isolated syndrome compared with healthy controls.[56] The duration of phase 2 trials in MS is frequently around 4–6 months, and OCT is unlikely to provide a reliable outcome during this timescale. From these data, one would expect that MS patients without optic neuritis will require follow-up for at least 2 years. The longitudinal monitoring of RNFL is technically challenging. Two methods have been validated clinically: topographic change analysis and statistical image mapping.[57–60] There is no consensus yet about how to obtain and analyse longitudinal OCT data in MS.

OCT and disability in MS

There are well characterised limitations to the clinical disability scales currently used in MS research,[61] not least of which is that they do not fully capture the range of disability seen in the disease, especially if they are not in the domain of patient mobility and motor function. Useful surrogate markers are challenging to validate. The driving force of disability in MS, axonal loss, seems to be associated with changes in the RNFL that are statistically related to changes in clinical disability progression (figures 3–5).[4–37] Because the RNFL is anatomically related to visual function, studies analysing this association were reviewed first. There are good arguments that RNFL loss also reflects neurodegeneration on a more global level,[2,3] stimulating additional review of the robustness of the association between RNFL loss and global clinical disability scales. During review of this research, an important consideration is that almost all of the studies to date have been done on group analyses.

Visual function

Visual acuity

Monocular visual acuity is usually assessed with standard eye charts. The method was introduced by the Dutch ophthalmologist Hermann Snellen in 1862.[62] The present convention is to document the Snellen equivalent (20/10–20/200). Snellen charts have methodological limitations, and of the many published improvements we will consider Early Treatment Diabetic Retinopathy Study (ETDRS) charts and low contrast acuity (Sloan charts).

Loss of RNFL was associated with reduced Snellen visual acuity in most[5,6,17,18,20,25,63–65] but not all[12] studies. A linear correlation between loss of Snellen visual acuity and RNFL thickness was reported in three studies.[17,63,64] The strongest correlations ($r>0·6$) were shown in studies including patients with MSON.[17,63,64] Similar results were obtained for use of standard Japanese decimal visual acuity.[33]

ETDRS charts

ETDRS charts have several advantages over the Snellen visual acuity charts, one being that the use of logarithmic scaling (logMAR) allows adjustment of the visual acuity

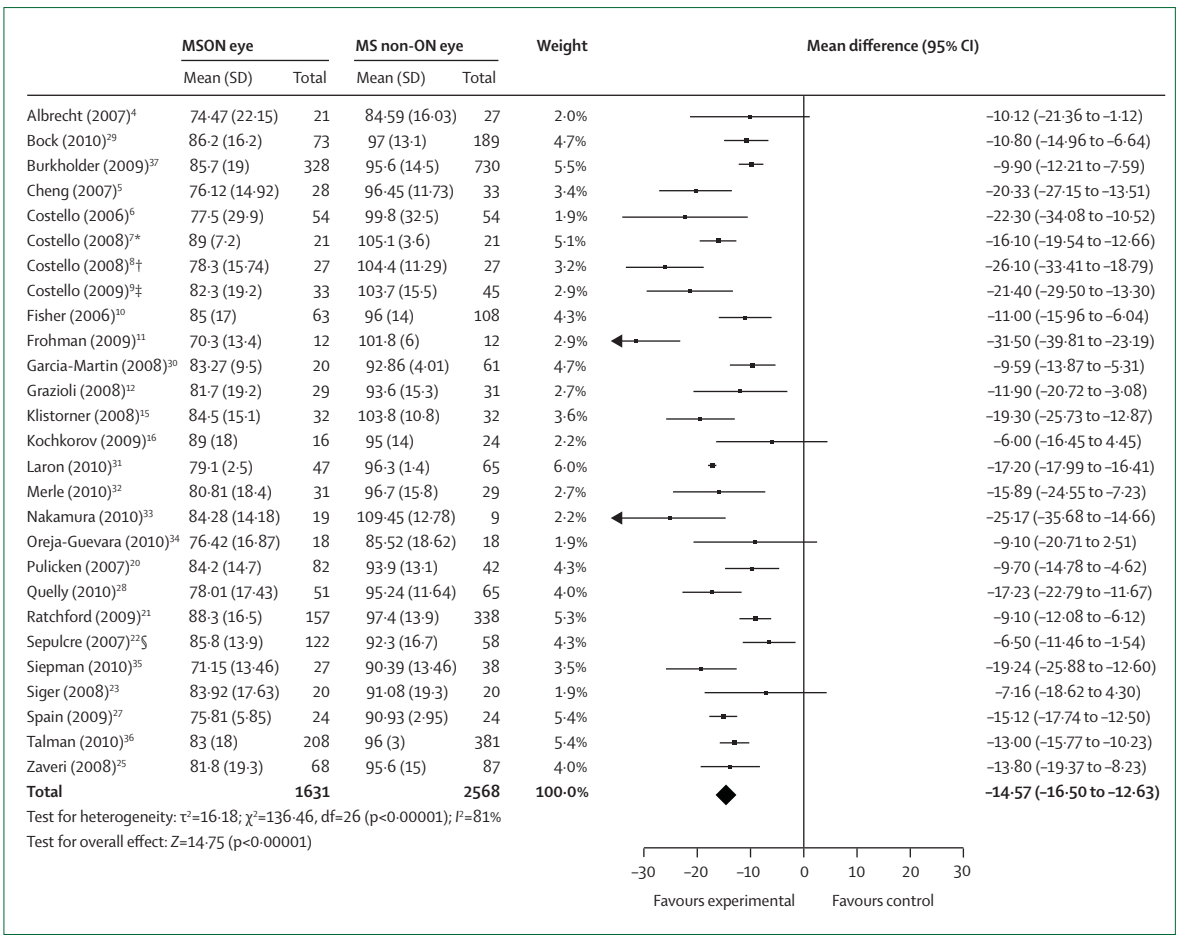

Figure 5: **Meta-analysis of OCT studies comparing ON-affected and unaffected eyes in patients with MS**
Overall averaged RNFL thickness and number of eyes investigated is shown. The difference between the ON-affected and unaffected eyes of patients with MS is smaller than the difference between MSON-affected eyes of patients and normal eyes of controls shown in figure 3 (NB, the scale of the x-axis differs between the two figures). OCT=optical coherence tomography. ON=optic neuritis. MS=multiple sclerosis. RNFL=retinal nerve fibre layer. *Data for 1 year after ON; the authors also present 2-year data, which were not included in this analysis. †Data for 1-year follow-up (13–18 months) were used; data for SD were provided by author. ‡1-year data for relapsing-remitting MS were included. §This study included 24 ON eyes and 98 eyes without ON; more details were not available from authors.

score to the viewing distance.[66] Essentially, a logMAR score provides interval data that facilitate statistical analyses and is therefore recommended for use in clinical trials.[67] Trip and colleagues[24] reported a linear correlation between the interocular difference in the logMAR score and RNFL thickness. Henderson and co-workers[14] confirmed the correlation between RNFL thickness and the logMAR score (r=–0·54, p<0·001). Costello and colleagues[7] also noted such a correlation 6 months after MSON. In a mixed cohort of untreated patients with MS, with or without optic neuritis, Spain and co-workers[27] reported a linear correlation (r=–0·53, p<0·001) that was consistent with the results of Siepman and colleagues[35] (r=–0·56, p<0·01).

Low-contrast letter acuity

Balcer and co-workers[68] first suggested integration of (binocular) low-contrast letter acuity (Sloane charts) into a modified multiple sclerosis functional composite on the basis of their observation that patients with MS could be significantly (p<0·0001) better distinguished from controls using this method at a 1·25% contrast level than with ETDRS charts. The authors also found Pelli–Robson charts to be of use (p=0·003). The results were confirmed in later studies.[36,69] Fisher and colleagues[10] showed a one-line change of 1·25% low-contrast letter acuity for every 4 µm of RNFL lost. A strong correlation between low-contrast acuity and RNFL thickness in eyes affected by MSON was described in two other studies (r^2=0·69, p=0·001;[11] r=0·54, p<0·001[25])—a finding confirmed independently in patients with primary progressive MS (for logMAR acuity r=–0·46, p=0·001, and Sloan 1·25% contrast acuity r=–0·34, p=0·024; note that r was squared in reference 11, accounting for the positive value, and reference 25 probably referred to an inverse correlation consistent with reference 14).[14] A moderate correlation between RNFL thickness and 2·5% charts (r=0·39, p<0·001) and 1·25% charts (r=0·31, p<0·001) was shown in one study.[20] In line with these

findings are those of Spain and colleagues[27] using 1·25% Sloan charts (r=–0·34, p=0·02). Currently, there are no longitudinal studies showing a good correlation between RNFL thickness and visual acuity over time.

Visual fields

MS can produce any type of visual field defect. The most common defects in acute MSON are dense but transient scotomas, which are central, altitudinal, or centrocaecal.[41,70,71] Achromatic static perimetry is typically used for assessment of visual field loss. The sensitivity of this technique is restricted when suprathreshold screening strategies are used and improves with threshold estimation strategies.[72,73] The likelihood of underestimation of visual field loss depends on the number of stimuli tested, stimulus size, the threshold loss, and the control of eye movements.

Costello and colleagues[6] used the central 30-2 full threshold strategy (Humphrey), which is sensitive and gives a good overview. The researchers identified an association between RNFL thickness and visual field loss at 3–6 months after optic neuritis. Below a threshold of 75 µm of RNFL loss, a linear correlation was found with the visual field mean deviation in dB. Mean deviation—one of four global indices provided by the Humphrey perimeter—gives the average of differences from normal expected value for the patient's age, and is useful for detection of diffuse visual field loss, as is the case in MSON. Importantly, there was no recovery of visual function in these patients. An RNFL thickness of less than 75 µm is regarded as a poor prognostic sign.[7,21,74] Costello and colleagues'[6] results are consistent with those of Trip and co-workers,[24] who described a linear correlation between the interocular difference in RNFL thickness and visual field mean deviation using the same protocol. A weak correlation between the averaged RNFL thickness and mean deviation was also confirmed by other investigators.[14,18,35,63] Noval and co-workers[63] described an association between RNFL loss and visual field loss at 1·5 and 3 months after MSON, but not after 6 months. They conclude that OCT might enable detection of RNFL damage at a level that is below the sensitivity of automated static perimetry, which is consistent with other studies.[19]

Cheng and colleagues[5] used a visual field severity score and found a better correlation between RNFL thickness and overall visual field loss compared with quadrant loss. They suggest that this finding could be attributable to diffuse rather than localised RNFL defects in MS or a poor structure-to-function map, causing restricted topographic correlations. Suboptimum image registration on TD-OCT in some patients offers an alternative explanation. Trip and co-workers[24] also failed to show an association between a temporal visual field defect and loss of RNFL thickness in the corresponding RNFL sector. They point out that the Humphrey 30-2 programme tests far fewer points in the nasal and temporal sectors than in the superior and inferior sectors, potentially leading to increased noise due to reduced sampling.

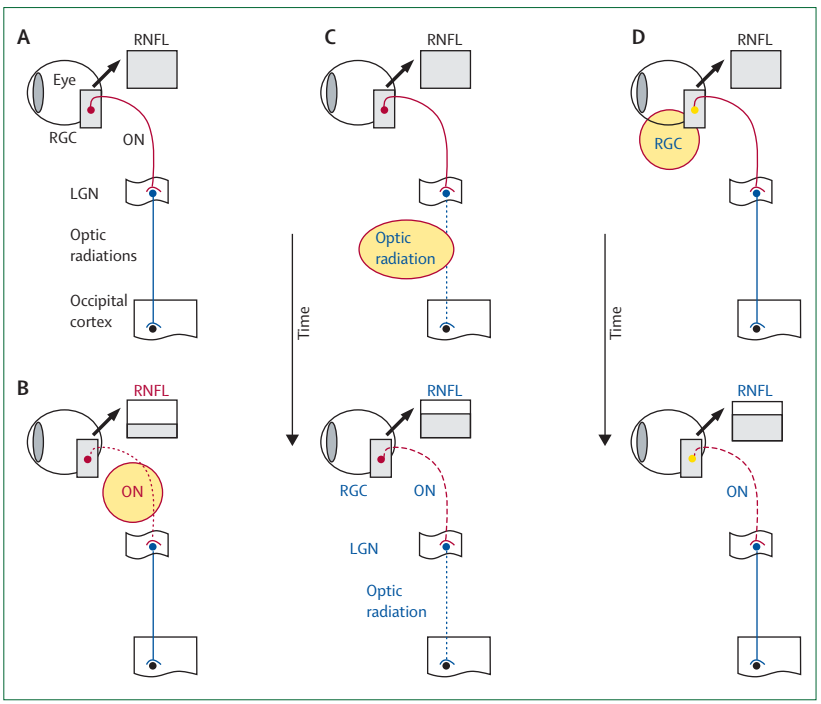

Figure 6: **A model of the presumed relation between RNFL thickness and MS pathology**
(A) A simplified sketch of the human visual pathway. RGCs send unmyelinated axons into the eye, where they form the RNFL (grey inlay), travel to the optic disc, and leave the orbit. Once the axons pass the sclera they become myelinated and form the ON. After passing through the chiasma, where the temporal fibres cross (not shown), they are called the optic tract. The optic tract wraps around the midbrain and enters the LGN, where all these axons synapse. After the LGN, the axons fan out through the deep white matter (optic radiations) to reach the occipital cortex. (B) In MS, optic neuritis directly causes acute axonal loss in the ON (red dotted line), leading to thinning of the RNFL (small grey box). (C) MS lesions within the optic radiations (blue dotted line) do not immediately result in RNFL thinning. This outcome is thought to be a chronic consequence of trans-synaptic axonal loss through the LGN. With time, trans-synaptic axonal degeneration causes a smaller amount of axonal loss in the ON (red dashed line), with a quantifiable degree of RNFL loss (grey box). (D) Progressive loss of RGCs (yellow dot) is a probable result of chronic changes in the anterior visual pathways themselves in MS, and causes a small amount of RNFL loss (grey box). Note that (C) and (D) both occur in the absence of optic neuritis. RNFL=retinal nerve fibre layer. MS=multiple sclerosis. RGC=retinal ganglion cell. ON=optic nerve. LGN=lateral geniculate nucleus.

Global clinical scores

EDSS

12 studies examined the relation between loss of RNFL and progression on the expanded disability status scale (EDSS).[4,9,10,12,17,22,23,26,35,64,75,76] An inverse correlation between RNFL thickness and the EDSS was reported in six studies (r=–0·348,[22] r=–0·7,[23] r=–0·399,[76] r=–0·30,[35] r=–0·42 in MS patients without optic neuritis,[4] and partial r=–0·35 using minimum RNFL thickness[75]). These data are consistent with results of two further studies describing a significant reduction of the RNFL with increasing EDSS percentiles.[10,12] Four studies did not identify an association between RNFL thickness and EDSS scores.[17,26,34,64] One of these studies included patients with neuromyelitis optica and MS,[17] and another presented detailed data for both variables, but did not include a correlation analysis.[9]

The differences in findings are at least partly accounted for by the heterogeneity of the groups investigated (figures 3 and 4). The strongest correlation between EDSS scores and RNFL thickness was found for eyes of patients

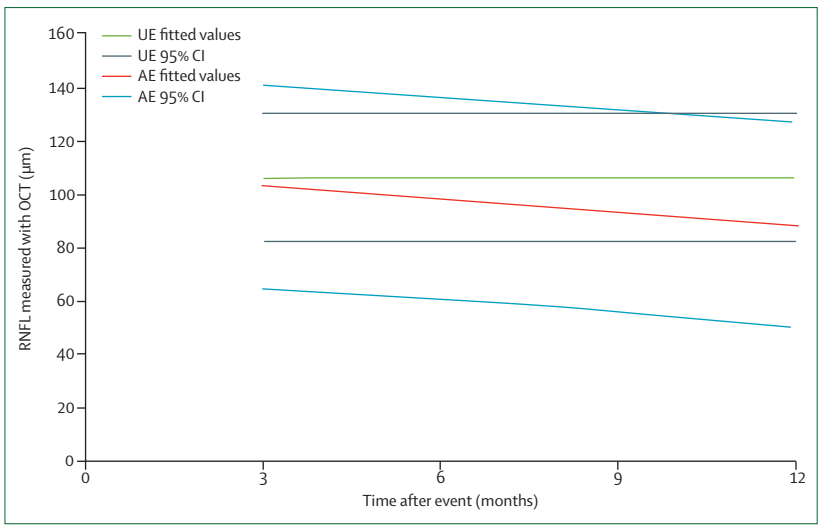

***Figure 7*: Longitudinal profile of OCT measurements of RNFL thickness in optic-neuritis-affected and unaffected eyes of patients with MS**

OCT=optical coherence tomography. RNFL=retinal nerve fibre layer. UE=unaffected eyes. AE=affected eyes. Modified from reference 7, by permission of Sage Publications.

with MS that were not affected by optic neuritis.[4,23] The strong effect of MSON on RNFL thickness (figure 3) could mask more subtle changes caused by either asymptomatic axon damage or trans-synaptic axonal degeneration in unaffected eyes of patients with MS.

Therefore, future treatment trials using OCT as a secondary outcome measure for global disability will have to anticipate that predefined analyses for patients without MSON are likely to be of stronger statistical power than for patients with MSON, and that alternative measures of disability that better reflect generalised neurological function, including cognition, might need to be used for indirect assessment of diffuse axonal loss in the CNS.

The multiple sclerosis severity score

The multiple sclerosis severity score was developed to overcome the problem of changes in the EDSS with different disease durations when comparing groups. There was no correlation between RNFL thickness and this score in one study including patients with MSON.[64]

OCT and electrophysiology in MS

OCT allows structural properties of the retina to be studied, thus complementing the many electrophysiological techniques aimed at functional assessment. Researchers have examined possible associations between the two domains. Recalling the simplified sketch from figure 6, one can formulate two key hypotheses to be tested. First, is there a relation between RNFL loss and VEP/pattern electroretinogram (ERG) amplitude reduction (figure 6B, D)? Second, does VEP evidence for demyelination in the context of normal anterior visual pathways predict later development of RNFL loss with trans-synaptic retrograde degeneration (figure 6C)?

VEP

After demyelination of the optic nerve, VEP latency is typically prolonged. This finding can persist for many years and is regarded as a sensitive but not specific test. In a longitudinal study, Brusa and colleagues[49] were first to note a small reduction of VEP amplitude in the unaffected eye of MS patients with optic neuritis, suggesting that this finding might be due to axonal loss. Advancing this idea, the same group showed that reduction of RNFL thickness was indeed related to reduced VEP amplitude (whole-field VEP and central-field VEP),[24] a finding confirmed by others.[15,18,19,77] Klistorner and co-workers[78] went on to show a high functional-topographic correlation between multifocal VEP amplitude and RNFL thickness (inferior visual field, r=0·84; superior visual field, r=0·78; central visual field, r=0·75; p<0·001 for all correlations). Advances in multifocal VEP data analysis might render this technique more accessible.[79] Several investigators[13,15,18,80] also identified a correlation between RNFL thickness and VEP latencies.

The association between reduction in RNFL thickness and VEP amplitudes lends further weight to the argument that demyelination-related damage to the optic nerve could either cause direct axon damage or might occur in the postgeniculate visual pathway, leading to retrograde axonal degeneration of the non-myelinated axons in the retina (figure 6B).

ERG

Using TD-OCT, Parisi and colleagues[80] noted a correlation between RNFL thickness and pattern ERG P50 latency as well as with the P50-P95 amplitude. This finding might be attributable to loss of ganglion cells after damage to the optic nerve.[80] Others did not find a convincing relation between overall averaged RNFL thickness and simple or multifocal ERG results,[13] possibly because multifocal ERG samples mainly the activation of photoreceptor and bipolar cells and not ganglion cells, and therefore a correlation might not necessarily be expected.

OCT and imaging in MS

The association between structural changes within the visual pathways as assessed by brain imaging techniques and OCT data was investigated in several studies included in our systematic review.[11,12,22,23,75,81,82] These investigators focused on optic-nerve imaging[11,81,82] and whole-brain imaging techniques.[11,12,22,23,45,75] The published data suggest correlations between RNFL thickness and measures of brain atrophy on MRI,[12,23,75] but a consensus has yet to emerge with respect to which atrophy measure is the most relevant, with grey matter atrophy remaining a hot topic.[11] Other MRI measures to be considered are normalised brain volume,[11,22] T2 lesion volume,[11,22,23] the magnetisation transfer ratio,[11,82] fractional anisotropy, and diffusion tensor imaging.[11,83] Less promising are T1 lesion volume[11,12,23] and mean parenchymal diffusivity.[11,45] For an in-depth review see reference 3.

Future developments

OCT and the macula in MS

Changes in macular volume, as well as inner and outer macular segments, consistently show volume loss caused by loss of RGCs.[12,14,18–21,24,30,35,37,74,84,85] All reported the macular volume was reduced in patients with MS compared with controls. Loss of macular volume was correlated with loss of RNFL in four studies.[14,24,37,81] Of note, retinal thickness in the macula is made up of many RGCs (cones in the macula have a 1:1 correlation with RGCs, whereas in the periphery many rods have a 1000:1 relation with RGCs). Therefore, the macula provides a model to test hypotheses about primary neuronal cell death followed by axonal loss. In an editorial,[86] Waxman asked three crucial questions. What are the mechanisms involved in RGC apoptosis? Could this be following axonal pathology or dysfunction? Alternatively, could RGC apoptosis be an example of primary neuronal injury independent from axonal damage? Longitudinal studies combining OCT fluorescence labelling and retinal layer segmentation with neuroimmunological methods (eg, targeted RGC antibody discovery) might be informative.

Polarisation-sensitive OCT

Specific tissue properties can be further investigated by recording the polarisation state of back-scattered light.[87,88] Polarisation-sensitive OCT (PS-OCT) yields depth-resolved information about any light polarisation changing properties of the sample related to tissue birefringence.[87,89–91] Importantly, birefringence of the RNFL is related to the structure of dominant axonal filaments such as neurofilaments and microtubules.[92] The birefringence of the RNFL induces a quantifiable degree of phase retardation.[89–91,93]

Cense and colleagues[93] showed that the birefringence of the RNFL is not constant, but varies by a factor of three around the optic-nerve head, with higher values reported in the superior and inferior quadrants, and lower values in the nasal and temporal quadrants. This property distinguishes the RNFL from other retinal structures, which are either polarisation preserving (eg, photoreceptor layer) or polarisation scrambling or depolarising (eg, retinal pigmented epithelium).[91] Because changes to the axonal cytoskeleton such as neurofilament compactness, phosphorylation, and stoichiometry can precede axonal loss,[94,95] there might be a chance to detect early stages of axonal pathology in MS with PS-OCT. Experimentally, change in RNFL birefringence has been shown to precede RNFL loss.[96]

Fluorescence labelling

Fluorescence labelling of a protein (annexin 5) that binds to a key component initiating apoptosis (phosphatidylserine) enables real-time in-vivo monitoring of RGC apoptosis.[97] Detection of apoptosing retinal cells provides a promising surrogate outcome for neuroprotective treatment strategies in glaucoma, dementia, and potentially MS.[98,99] Analogously, labelling of mitochondria could enable in-vivo testing of the virtual hypoxia hypothesis in MS.[100]

Retinal sector analysis

This review did not include OCT data for sector analysis of the retina. One can postulate that retinal axons of some retinal sectors are more vulnerable than others in MS. Therefore, quantitative analysis of these sectors might allow for sensitive detection of axonal loss. However, there is a large normal variation in the appearance of the optic disc affecting the RNFL thickness, which ought to be controlled for.[101,102]

RNFL thickness and reflectivity maps

Use of individual circular RNFL scans at the optic-nerve head to accurately localise focal and peripheral loss of retinal axons is challenging. One possible approach is the development of RNFL thickness maps.[90] Because the loss of retinal axons in MS is more diffuse than the arcuate bundle loss seen in glaucoma, an integrative approach combining PS-OCT data with RNFL thickness maps could have the potential to predict the topography of RNFL loss in MS.

Retinal layer segmentation algorithms

With the introduction of SD/FD-OCT, retinal layer image quality potentially allows for segmentation and quantification of individual layers. There is histological evidence that MS affects not only the RNFL, but also cellular layers.[40] Therefore, new segmentation algorithms for quantitative analyses of individual retinal layers might enable us to better investigate progression of neurodegeneration in MS.

Doppler OCT and vascular changes in MS

There is some evidence that vascular comorbidity is a poor prognostic sign in MS.[103] Changes in the retinal vasculature such as perivasculitis are recognised in MS. Perivasculitis leads to extravascular hyaline deposits, hence the descriptive name, vascular sheathing. These changes are likely to lead to increased rigidity of retinal vasculature and thus rapid pulse propagation from the posterior (choriodal) to the anterior (retinal vasculature) circulation.[16] This idea could be investigated by combination of SD-OCT with Doppler velocimetry. This technique is non-invasive and allows for accurate topographic localisation of retinal blood vessels.

Optical coherence microscopy and action potentials

The effect of action-potential propagation on light properties was recognised by Frank,[104] who cited his work together with Kornakova[105] in 1947. The field flourished over the next 30 years.[106] With optical coherence microscopy, the structural assessment of an action potential became a reality.[107,108] At present, only in-vitro monitoring of action-potential propagation is possible.

Functional imaging of the human retina in vivo would be highly desirable to investigate whether axonal dysfunction precedes RGC or RNFL loss.

Conclusions

There is much excitement about OCT in MS research, and as one of the first neurologists to make extensive use of the ophthalmoscope, Hughlings Jackson (1835–1911), said: "It is not too much to say that, without an extensive knowledge of ophthalmology, a methodological investigation of diseases of the nervous system is not merely difficult, but impossible."[109] OCT is a new and promising technique that has potential for monitoring of treatment effects in trials of neuroprotective strategies in MS. First, there is a clear pathological correlate (axonal loss). Second, the analytical reproducibility is excellent. Third, the sensitivity to change is twice as high as the normal physiological changes during ageing and more than an order of magnitude greater than the averaged changes seen after optic neuritis. Fourth, OCT is of high clinical relevance, correlating with clinical measures (loss of visual function), thus capturing a fundamental feature associated with disability progression. Fifth, data from brain imaging and electrophysiological studies suggest that the integration of OCT into MS research could allow a more accurate view of structure–function relations in understanding of the pathophysiology of this enigmatic disease. Finally, OCT is predictive of a clinical outcome (poor visual recovery). We propose that the role of OCT in future MS research should be investigated by an international workforce with a concentrated, resource-saving approach.

Contributors

AP conceived the idea for this review, did the literature search, systematic review, and meta-analysis, and wrote the first draft of the report. JFdB and RK revised the report and did independent literature research. SS, PV, AG, PAC, and CP revised the report.

Conflicts of interest

AP has received consulting fees from Novartis. PV has received honoraria from Heidelberg Engineering. SS has received research grants from Biogen Idec and Bayer Schering Pharma and consulting fees from Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis. AG has received payment for services from Biogen Idec and Applied Clinical Intelligence for work on a clinical endpoint adjudication committee related to clinical trials of daclizumab and from Projects in Knowledge for editorial work on CME-related publications. He has also received honoraria from Novartis Pharmaceuticals and PROCE CME. PAC has received grants from Biogen Idec, Teva, Vertex, Bayer, Genentech, and Serono and consulting fees from Novartis, Biogen Idec, Teva, Vertex, Novo Nordisk, Centacor, Serono, and Genentech. CP has received institutional grants from Novartis, Biogen Idec, Bayer Schering, GlaxoSmithKline, UCB, Merck Serono, and Teva, consultancy fees from Actelion, Biogen Idec, Bayer Schering, Teva, Merck Serono, Novartis, GlaxoSmithKline, UCB, Roche, Antisense Therapeutics, and has provided expert testimony for Biogen Idec. SS, PV, RK, AG, PAC, and CP sit on the Novartis steering committee for a multicentre observational study, and receive honoraria. JFdB has no conflicts of interest.

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