

Controversies in multiple sclerosis

OCT should be part of the routine monitoring of patients with MS- No

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Optical coherence tomography (OCT) is an exciting technique that has been applied to multiple sclerosis (MS) research for around the last ten years. OCT enables rapid, non-invasive *in vivo* measurement of retinal nerve fibre layer (RNFL) thickness, reflecting neuroaxonal density within the optic nerve. Early studies applied to post-acute optic neuritis [1] demonstrate neuroaxonal loss. Further research extended the scope of OCT, finding that its measures appeared to be a useful surrogate of generalised brain axonal loss in MS patients; progressive RNFL thinning was evident even in the absence of a history of optic neuritis [2], and RNFL thickness was associated with cerebral volume measurements [3]. RNFL thinning is evident in patients with secondary progressive MS [4], but also earlier in the disease course in clinically isolated syndromes [5] and in forms of MS with minimal disability [6]. RNFL thickness shows clinical correlations with disability measures such as visual acuity [1] and extended disability status scores (EDSS) [3].

These studies have established OCT as an important research tool. It appears a useful biomarker of axonal loss, the pathological correlate of MS disease progression, leading some to advocate routine monitoring of MS patients with OCT. They argue that OCT is a simple, non-invasive and inexpensive method of identifying axonal loss, more sensitive than clinical assessment and cheaper than magnetic resonance imaging (MRI). However, we believe their arguments are fundamentally flawed.

Currently, patients with MS are monitored by history, examination and simple clinical assessments such as EDSS and timed walks. The diagnosis of progression is made on clinical grounds; a change in the pattern of disease from relapses and remissions to progressive gradual deterioration in mobility is typical. The benefit of identifying non-relapsing secondary progression is that unnecessary exposure to disease-modifying therapy can be prevented; patients avoid injections and treatment side effects, hospitals reduce treatment and associated blood monitoring costs. Whilst OCT may detect subclinical progression before it is clinically evident, this would not influence management; the presence of RNFL thinning in a patient with a clinically isolated syndrome would not preclude disease-modifying treatment for relapses. Clinical evaluation remains the key to effective management; OCT would not contribute.

OCT expenses are not negligible- an OCT machine costs around \$70,000 [7] and technicians with expertise to operate it, also carry a cost. This is certainly cheaper than magnetic resonance imaging (MRI), but this is not a meaningful comparison because MRI is not necessary in routine monitoring of MS patients either; its principle role is diagnostic and for confirmation of clinically aggressive inflammation necessitating escalation of disease-modifying therapy. OCT would fulfill neither of these roles.

OCT can estimate brain axonal loss and be considered a screening test for this aspect of MS pathology. As a screening test, all of the usual criteria must be fulfilled before general application can be recommended.

A screening test must be easily applicable to pre-symptomatic patients and of low risk; OCT fulfills these criteria. Costs have already been discussed. Sensitivity and specificity are more problematic; one large study reported that RNFL thinning was detectable in at least one eye in only 34% of MS patients [8], and associations between optic nerve and generalised brain axonal loss are weakened by a previous history of optic neuritis [9] or lesions elsewhere in the visual pathway [10]. OCT measurements are also affected by non-MS ocular conditions (e.g. retinal problems, optic disc drusen, glaucoma, cataracts, high myopia) and therefore will potentially be valid for only a subset of MS patients' eyes, when these confounding factors are absent. Hence it becomes difficult to advocate its *routine* use.

Furthermore, the term 'routine monitoring' implies the ability to accurately detect longitudinal changes. OCT analyses of large groups of MS patients have reported annual RNFL thinning rates of 1-2 $\mu\text{m}/\text{year}$ in non-ON eyes. The largest longitudinal study (examining 299 MS patients) using time-domain OCT found that these reductions became statistically significant at least two years after baseline measurements [2]. A more recent longitudinal study of 133 relapsing-remitting MS patients, using spectral-domain OCT, showed similar rates of RNFL thinning [11] with quite wide variability. Although ganglion cell-inner plexiform layer thinning showed less variation than RNFL, the magnitudes of change were smaller still (approximately 0.5 $\mu\text{m}/\text{year}$). A recent report on consensus criteria for retinal OCT (OSCAR-IB) highlighted certain factors to take into

account to assess OCT quality [12]. These factors can influence scan-rescan reliability. For example, off-centre beam placement can introduce measurement errors of up to 10 μm , well in excess of the expected disease effect of 1-2 $\mu\text{m}/\text{year}$ seen in MS patients. It is therefore unlikely that even spectral-domain OCT can reliably detect longitudinal changes of such small magnitudes in individual patients.

Another important reason that OCT monitoring cannot be recommended in clinic is that neuroaxonal loss in MS does not dictate therapeutic management. Early identification is therefore not beneficial, either to individual patients, because there is no influence on management, or to society, because there is no translatable public health impact.

So, OCT is not indicated for clinical monitoring, but what about diagnosis and prognosis? Could OCT contribute to diagnostic criteria by demonstrating early evidence of subclinical optic nerve involvement in the manner of visual evoked potentials (VEPs)? This is unknown. Many clinicians already use VEPs sparingly in diagnosis of MS; with the advent of MRI they have assumed an increasingly peripheral role. Although, like VEPs, OCT might be occasionally diagnostically useful in individuals (for example, a patient with a history of recurrent optic neuritis but otherwise normal history, examination and imaging), there are no studies comparing the two techniques and diagnosis does not appear the greatest area-of-need.

Some might argue that identifying early axonal loss could guide prognosis. However, this is far from clear. There is great inter-individual variability in prognosis even amongst clinically progressing patients. The effect on prognosis of early axonal loss in a clinically well patient is unknown at present, and so the finding only increases uncertainty for both patient and doctor. The very fact that patients with early and benign MS have evidence of axonal loss is an argument against the use of OCT as a prognostic tool; there is clearly imperfect correlation between RNFL and clinical status.

In summary, it is undeniable that OCT represents an important addition to our armamentarium of research tools in MS. A biomarker of axonal damage will be invaluable in ongoing trials of experimental therapies for patients with primary and secondary progressive MS, one of the most important areas-of-need in the field. However, OCT cannot yet be recommended as a routine clinical monitoring tool. In the current financial climate, it is more important than ever for guidelines and recommendations to be evidence-based. The routine provision of OCT machines for clinics cannot be considered an acceptable use of limited National Health Service resources until there are tangible benefits for patients; this first requires available disease-modifying treatments for patients with progressive MS.

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