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REVIEW

Measures of visual pathway structure and function in MS: Clinical usefulness and role for MS trials

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Abstract
Over the past decade, the visual pathway in multiple sclerosis (MS) has become an important system for assessing both patient function and disease burden. Abnormalities of low-contrast acuity, long recognized as important correlates of driving, facial recognition, and other activities of daily living, are now noted to be common among patients with MS, even among those with no history of acute optic neuritis (ON). Low-contrast letter acuity scores correlate well with brain MRI lesion burden, visual-evoked potential (VEP) amplitudes, health-related quality of life (QOL), and retinal nerve fiber layer (RNFL) axonal and neuronal loss as measured by optical coherence tomography (OCT). Axonal and neuronal degeneration in MS is likely to be an important cause of visual impairment and disability, particularly among patients with progressive MS subtypes. With the advent of OCT and the use of low-contrast letter acuity charts in MS research and clinical trials, the structure–function correlations afforded by the anterior visual pathway can be assessed and potentially harnessed as a model for testing new therapies. Recent advances in OCT, such as high resolution spectral-domain techniques and computerized algorithms for image analysis, have allowed for measurement of specific retinal layers, including the ganglion cell (GCL) neuronal layer and its intimately associated, thin layer of interneurons, the inner plexiform layer (IPL). Longitudinal collaborative studies of GCL+IPL thinning and RNFL axonal loss are providing an in vivo view into neuroretinal pathology, and are providing new insights into how the visual pathway may reflect overall mechanisms of disease in MS.

Contents

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1. Aim of this review

This review will discuss the use of functional and structural visual outcome measures in MS. Low-contrast letter acuity testing has become an important visual assessment tool in clinical trials. More recent studies have highlighted the potential for OCT RNFL and GCL+IPL thickness to serve as structural markers for neuroprotection and repair. We will examine how studies of vision in MS may provide clinical applications by reviewing data for low-contrast letter acuity, high-contrast visual acuity (VA), OCT measures, and QOL scales in patients with MS (Table 1). Comparisons of eyes of patients with MS with and without a history of acute ON, and the relation to disease-free control data, will provide a perspective on the afferent visual pathway in MS based on group data. The information provided in Table 1 represents a culmination of a decade of investigation, and can serve as a basis for ''reference ranges,'' so to speak, for the various structural and functional measures. Application of these data to individuals should be done with caution given the inherent difficulties of applying group data to single patients, but this review provides a start for discussing the overall picture of vision in MS.

2. MS and vision

2.1. Background

Studies of vision in MS evolved from the necessity to expand clinical outcome measures for MS treatment trials (Balcer, 2001). Until the 1990s, clinical trials of MS treatment included only the Extended Disability Status Scale (EDSS) as a measure for treatment efficacy. Widely used, the EDSS was somewhat limited by its scores heavily weighting ambulation and generally lacking sensitive visual and cognitive components. Given a need for more sensitive outcome measures, the National MS Society Clinical Outcomes Assessment Task Force developed the MS functional composite (MSFC) which included the timed 25-foot walk, 9-hole peg test, and Paced Auditory Serial Addition Test (Rudick et al., 1997; Rudick et al., 1996). While these performance measures captured several important dimensions of function in MS, the only candidate vision test in the clinical trial datasets was high-contrast (black on white) visual acuity (VA), assessed using non-standardized Snellen charts or near cards. Since these measures of VA lacked sensitivity to change over time in the clinical trial datasets used to develop the MSFC, alternative candidate visual function tests were considered. Data from the Optic Neuritis Treatment Trial (ONTT) showed that patients with ON had persistent abnormalities of contrast sensitivity by Pelli–Robson charts even among affected eyes that recovered high-contrast VA to 20/20 or better (Optic Neuritis Study Group, 2008; Beck et al., 2004; Cleary et al., 1993; Trobe et al., 1996; Volpe, 2008; Keltner et al., 2010; Ashworth et al., 1989; Bodis-Wollner and Brannan, 1997; Regan et al., 1981; Wender, 2007; Kupersmith et al., 1984). Since the Pelli–Robson contrast sensitivity charts were temporarily out of print briefly when studies to develop new MS trial visual outcomes were initiated, low-contrast letter acuity charts (Sloan charts) were selected for further study (Fig. 1).

2.2. Low-contrast letter acuity

Investigations during the past decade have demonstrated that low-contrast letter acuity is a sensitive measure of visual function. As illustrated by the collective data in Table 1, patients with MS have shown significantly reduced low-contrast acuity scores compared with disease-free controls; this is true for both binocular (testing with both eyes open) and monocular measurements. Reductions of low-contrast letter acuity are evident even in eyes of patients without a history of ON. Given these clear differences that have been consistent over a decade of observation, assessment of low-contrast letter acuity in clinical practice may be helpful in determining the efficacy of treatment and monitoring the disease course in patients. Importantly, scores for low-contrast acuity correlate with vision-specific QOL, linking visual impairment to loss of function in patients with MS (Table 1). As such, low-contrast acuity scores may give clinicians insight into the physical capabilities and activity limitations of both groups and individual patients with MS.

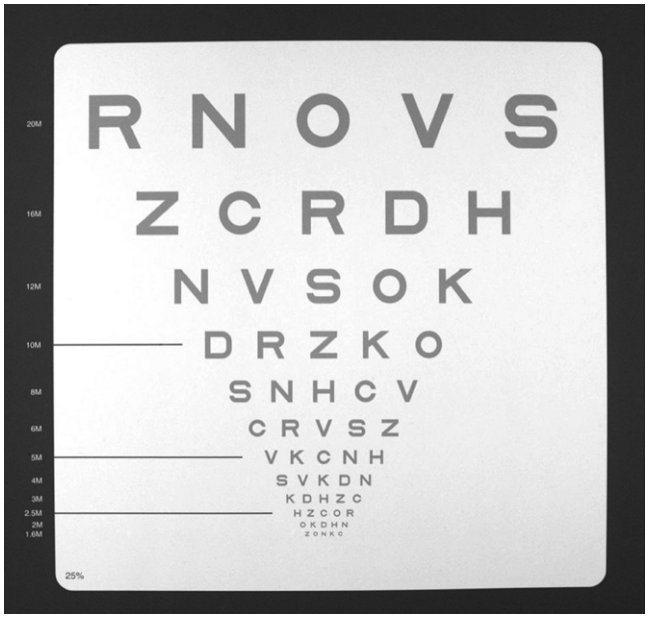

Fig. 1 Low-contrast letter acuity chart (low-contrast Sloan letter chart, Precision Vision, LaSalle, IL). * These charts have a standardized format based on Early Treatment Diabetic Retinopathy Study visual acuity charts, the standard used in ophthalmology clinical trials, and have several advantages over standard Snellen charts or near vision testing cards as traditionally used in MS trials: (1) letters (Sloan letters) are designed to be equally detectable for normal observers; (2) each line has an equal number of letters (five per line); (3) spacing between letters and lines is proportional to the letter size; (4) change in visual acuity from one line to another occurs in equal logarithmic steps (change of three lines constitutes a doubling of the visual angle); (5) visual acuity (for high-contrast [black letters on white] chart) may be specified by Snellen notation for descriptive purposes (i.e., 20/20), by the number of letters identified correctly. This figure shows the 25% contrast level for purposes of illustrating format; the actual contrast levels used in these trials, 2.5% and 1.25%, have substantially lighter gray letters. The charts measure 14×14 in. for easy use and portability in the MS clinical trial setting; charts may also be mounted on a retroilluminated cabinet, thus eliminating the need for standardization of room lighting levels. Reprinted with permission from Balcer et al., 2007;68:1299–1304 (9).

The MS Progressive Avonex Clinical Trial (IMPACT) was the first clinical trial to use low-contrast letter acuity as an exploratory visual outcome (Balcer et al., 2003; Baier et al., 2005; Balcer et al., 2000; Balcer and Frohman, 2010; Balcer et al., 2007). The low-contrast Sloan letter charts have a format similar to the Early Treatment Diabetes Retinopathy Study (ETDRS) chart, the standardized charts used to assess high-contrast VA in ophthalmology clinical trials. Both ETDRS and Sloan low-contrast acuity charts contain rows of 5 letters per line; to provide a continuous measure, the score for each chart is the number of letters identified correctly. Reliability studies of both ETDRS VA and low-contrast letter acuity have shown that differences of 5 letters (for VA) and 7 letters (for low-contrast acuity) are beyond those expected for test-retest variability and are therefore likely to be clinically meaningful (Rosser et al., 2003; Beck et al., 2007; Balcer et al., 2000; Talman et al., 2010; Cettomai et al., 2008). Table 1 illustrates the difference in mean letter score to be ≥ 5 letters for VA and ≥ 7 letters for low-contrast acuity in MS patients as compared to disease-free controls. The clinical significance of these differences has been emphasized by findings indicating that such visual loss or improvement correlates with both QOL scores and OCT measures of axonal and neuronal loss.

The IMPACT trial showed that low-contrast letter acuity correlated with disability in MS that was not captured by high-contrast VA or ambulation status (Baier et al., 2005). Low-contrast acuity as an exploratory outcome in IMPACT showed that lower (worse) low-contrast acuity scores were associated with worse performance on the MSFC and EDSS (Balcer et al., 2003). Low-contrast letter acuity also showed high inter-rater reliability (high intraclass correlations of 0.86–0.95) in a heterogeneous MS cohort (Balcer et al., 2000). These data provided the initial evidence that low-contrast visual acuity was capable of capturing MS related dysfunction not previously captured by EDSS and MSFC.

Subsequent studies showed that, compared to disease-free controls, patients with MS had worse scores for low-contrast letter acuity; these investigations also demonstrated that low-contrast acuity was the visual function test that best distinguished patients vs. controls, accounting for age (Baier et al., 2005; Balcer et al., 2003) (Fig. 2). As a tertiary outcome in the phase 3 trial of natalizumab vs. placebo (AFFIRM) (Balcer et al., 2007), low-contrast letter acuity captured treatment effects and changes over time. Data showed a reduction of the cumulative probability of sustained visual loss (47%, $P<0.001$ for 2.5% contrast level) and sustained clinically meaningful visual improvement (by 57%, $P=0.01$) in the natalizumab treated patients (Balcer et al., 2007). High contrast VA did not show significant changes or detect differences over time between the placebo and active treatment groups.

Although initial analyses of AFFIRM trial data used 10-letter (2-line) differences in both low-contrast acuity and VA scores as criteria for clinically meaningful visual loss, these thresholds have been subsequently redefined based on test-retest reliability studies, resulting in criteria of 7 letters on low-contrast and 5 letters on VA charts (Talman et al., 2010). Furthermore, these thresholds of clinically meaningful difference in correlate well with RNFL and GCL+IPL thicknesses and with QOL measures, and have thus been carried forward in longitudinal analyses of MS vision research and clinical trial data (Talman et al., 2010).

2.3. Vision specific quality of life

Low-contrast letter acuity scores have been shown to be lower (worse) in patients with reduced vision-specific and overall QOL. Patients with MS showed significant reductions in scores on the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) compared to disease-free controls (Table 1) (Ma et al., 2002; Raphael et al., 2006; Mowry et al., 2009). Two-line reductions in low-contrast acuity were associated with 4-point worsening in NEI-VFQ-25 composite scores, accounting for age

Table 1 Mean reference values from recent investigations of vision, QOL, and OCT in MS.

	Disease-free controls	All MS	MS, no history of on	MS, history of on	References for data *
High-contrast visual acuity (VA), ETDRS, number of letters correct	64±5 (*n*=61 eyes)	59±8 (*n*=239 eyes)	60±6 (*n*=150 eyes)	58±9 (*n*=87 eyes)	103 (22,47,56,81,84)
Binocular testing	66±5 (*n*=324 pts)	62±8 (*n*=1007 pts)	63±7 (*n*=544 pts)	61±10 (*n*=463 pts)	56 (7-10,51)
Low-contrast letter acuity (2.5%), number of letters correct	34±8 (*n*=61 eyes)	26±11 (*n*=239 eyes)	28±9 (*n*=150 eyes)	22±12 (*n*=87 eyes)	103 (22,47,56)
Binocular testing	43±6 (*n*=324 pts)	36±10 (*n*=1007 pts)	38±9 (*n*=544 pts)	35±11 (*n*=463 pts)	56 (7-10,51)
Low-contrast letter acuity (1.25%), number of letters correct	25±7 (*n*=61 eyes)	16±10 (*n*=239 eyes)	18±10 (*n*=150 eyes)	11±11 (*n*=87 eyes)	103 (22,47,56,81,84)
Binocular testing	34±8 (*n*=324 pts)	24±11 (*n*=1007 pts)	26±11 (*n*=544 pts)	22±12 (*n*=463 pts)	56 (7-10,51)
NEI-VFQ-25 composite score, best score=100	96±4 (*n*=31 pts)	88±13 (*n*=122 pts)	90±12 (*n*=111 pts)	85±14 (*n*=51 pts)	103 (49-51,56)
10-item neuro-ophthalmic supplement to the NEI-VFQ-25, best score=100	97±3 (*n*=31 pts)	87±13 (*n*=122 pts)	88±12 (*n*=111 pts)	83±14 (*n*=51 pts)	103 (49-51,56)
Time-domain (TD) OCT					
Peripapillary RNFL thickness (μm)	104.5±10.7 (*n*=219 eyes)	92.5±16.7 (*n*=1058 eyes)	95.6±14.5 (*n*=730 eyes)	85.7±19.0 (*n*=328 eyes)	81 (20-22,47,70-84)
Total macular volume (mm^3)	6.84±0.36 (*n*=219 eyes)	6.54±0.51 (*n*=1058 eyes)	6.63±0.48 (*n*=730 eyes)	6.36±0.53 (*n*=328 eyes)	81 (20-22,70-84)
Spectral-domain (SD) OCT					
Peripapillary RNFL thickness (μm)	92.9±10.0 (*n*=61 eyes)	84.3±12.8 (*n*=239 eyes)	87.6±11.1 (*n*=150 eyes)	78.4±13.6 (*n*=87 eyes)	103 (96,105)
Ganglion cell+inner plexiform layer (GCL+IPL) (μm)	88.9±6.9 (*n*=61 eyes)	84.1±8.4 (*n*=239 eyes)	87.0±6.6 (*n*=150 eyes)	79.7±9.2 (*n*=87 eyes)	103 (96,105)
Macular RNFL (μm)	29.6±6.0 (*n*=61 eyes)	23.5±8.2 (*n*=239 eyes)	25.5±7.1 (*n*=150 eyes)	20.0±9.0 (*n*=87 eyes)	103 (96,105)

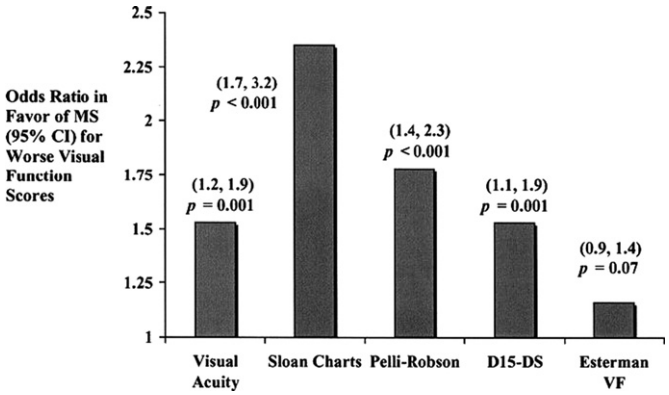

Fig. 2 Logistic regression analyses demonstrating capacity for each visual function test to predict multiple sclerosis (MS) vs disease-free control status in a heterogeneous MS cohort, accounting simultaneously for age. Odds ratios in favor of participants with worse vision scores being MS patients (vs disease-free controls) were greatest for low-contrast letter acuity (Sloan charts) and contrast sensitivity (Pelli–Robson chart). These measures thus best distinguish MS patients from disease-free control subjects, even after accounting for age differences between the two groups. VF=visual field. Reprinted with permission from Balcer et al. Neurology 2003;61:1367–1373.

($P<0.001$) (Mowry et al., 2009; Submacular Surgery Trials Research Group, 2007; Submacular Surgery Trials Research Group, 2003; McKean-Cowdin et al., 2007; Globe et al., 2004a,b). As shown in Table 1, differences in mean scores between MS patients and controls were ≥ 4 points, a difference that is considered clinically significant based on epidemiologic studies (Submacular Surgery Trials Research Group, 2007; Submacular Surgery Trials Research Group, 2003). The use of QOL measures is considered important by both investigators and regulatory agencies for determining the efficacy of MS therapies, and for judging the clinical meaningfulness of outcomes such as low-contrast acuity and OCT measures.

In order to better capture QOL as it relates to vision in MS, a 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 was designed by our research group using groups of patients with symptoms related to ON and MS. Scores for the 10-Item Supplement capture efferent as well as afferent aspects of visual dysfunction in MS, and correlate well with binocular scores for low-contrast acuity and VA ($P<0.001$). In addition, binocular low-contrast acuity scores are lower among MS patients with worse vision-specific QOL by the Impact of Visual Impairment Scale (visual sub-scale of the MS Quality of Life Inventory [MSQLI], abbreviated IVIS, $P<0.001$) and with overall health-related by the SF-36 Physical Components Summary, the generic core of the MSQLI ($P<0.001$) (Mowry et al., 2009). The relation of low-contrast letter acuity to QOL underscores the capacity for vision to capture MS-related disability (Miller et al., 2010).

2.4. Binocular summation

The introduction of OCT into MS vision research as a structural marker of axonal and neuronal loss in the retina has necessitated the use of monocular vision testing in addition to the binocular testing that has the advantage of capturing visual function with both eyes open as is present for daily activities. Functioning under both monocular and binocular conditions has important implications for MS patients, and there is evidence from previous literature that vision scores with both eyes open may be better than those for either eye separately (binocular summation). This is evident in large MS cohorts as seen in Table 1 (Pineles et al., 2011). In this heterogeneous patient group (1007 patients and 324 disease-free controls), binocular scores were 5–7 letters better than monocular eye acuities (28–52% with >7 letters, $P<0.001$) for low-contrast acuity at the 2.5% and 1.25% levels. By comparison, only 3.0–3.4% of patients showed similar degrees of summation for high-contrast VA. A history of ON in one or both eyes ($P=0.015$), greater discrepancy between VA of the two eyes ($P<0.0001$) and age ($P<0.0001$) were associated with less binocular summation, and history of ON in particular was associated with binocular inhibition. This study also found that greater degrees of binocular summation were associated with improved QOL scores on both the NEI-VFQ-25 ($P=.02$) and the 10-Item Supplement ($P=0.03$) (Pineles et al., 2011). Thus, binocular summation is another important marker for disability in patients with MS because it can capture how patients with MS perform in daily life activities.

2.5. Relation of vision to MRI

Structural markers, such as MRI, are necessary for establishing validity of clinical outcome measures. While low-contrast vision likely best reflects MS disease in the optic nerves and other anterior visual pathway structures, the posterior visual pathway is a less well studied region in MS that has been shown to have relevance to the perception of low-contrast targets. The relation of low-contrast letter acuity to MRI abnormalities in the post-geniculate visual pathway has been elaborated through the use of MRI. In one study, binocular low-contrast acuity scores were lower (worse) among patients with greater degrees of brain atrophy (lower brain parenchymal fraction); these correlations were stronger than those for high contrast VA (Baier et al., 2005). Another study demonstrated a correlation between low-contrast letter acuity to T2 lesion burden

throughout the brain (2.5% contrast level: adjusted R^2 0.26, P=0.004; 1.25% contrast level: adjusted R^2 0.25, P=0.002; VA: adjusted R^2 0.17, P=0.04), as well as the post-geniculate pathway and optic radiations via MRI (Wu et al., 2007). In this study, 5- letter reductions in low-contrast letter acuity corresponded to 3-mm^3 increases in T2 lesion volume throughout the brain.

2.6. Relation of vision to visual evoked potentials

Visual evoked potentials are electrophysiological measures of afferent visual pathway integrity, and complement low-contrast letter acuity testing. While axonal loss can alter the amplitude of the VEP, VEP latency in MS is often prolonged (Halliday et al., 1973; Hoeppner and Lolas, 1978). The changes in VEP in MS may be helpful in diagnosing subclinical manifestations of disease, including demyelination and axonal loss. VEPs using low-contrast images, in comparison to high-contrast checkerboard patterns, may be more sensitive in detecting abnormalities (Kupersmith et al., 1984; Thurtell et al., 2009).

Naismith et al. (2009) evaluated OCT and VEPs as measures of visual pathway structure and function. A total of 65 patients with demyelinating disease, all of which had at least on prior episode of ON $\geq$6 months prior to enrollment, were entered into the study. The study showed that OCT RNFL sensitivity after ON was 60% while VEP sensitivity was 81% (P=0.002). VEPs were also able to identify 75% of all subclinical eyes while OCT identified $<$20%. Data from this study illustrate the complementary nature of OCT and VEP for identifying important features of visual pathway disease in ON and MS. These investigations also point out the need for large scale normative data to use when interpreting structural and functional MS visual outcomes. The disease-free control data in Table 1 provide a starting point for judging the normative ranges for both controls and patients with MS.

3. MS and OCT

3.1. Background

In 1974, Frisén and Hoyt first described thinning of the retinal nerve fiber layer (RNFL) in patients with MS (Frisén and Hoyt, 1974). Post-mortem studies later confirmed the suspicion that atrophy was occurring in the RNFL in nearly 71% of the patients studied (Kerrison et al., 1994). The invention of optical coherence tomography (OCT) has allowed for objective measurement of the layers of the retina in vivo (Frohman et al., 2008a, 2006, 2008b). While acute demyelination as a result of ON is an important contributor to visual loss, axonal and neuronal degeneration in the anterior visual pathway likely to be important contributors to visual dysfunction in MS, even in patients without an acute ON history (Frohman et al., 2008a Trapp et al., 1998; Evangelou et al., 2001; DeLuca et al., 2006; Sepulcre et al., 2009; Green et al., 2010)

Because thinning of the RNFL and GCL+IPL by OCT are associated with reductions in visual function and QOL, OCT measures of axonal and neuronal loss have a unique ability to capture structure-function correlations in MS. Table 1 shows a mean difference in RNFL thickness of 11.8 μm between disease-free control and all MS eyes (with and without a history of ON). The ability of OCT to detect these differences supports its potential role as a structural marker in MS clinical trials. OCT provides a non-invasive, objective measure of visual pathway integrity, and therefore could be used to determine effectiveness of neuroprotective and other MS therapies. Further, OCT can be used in conjunction with visual function testing to follow disease progression of patients with MS.

3.2. Features and advantages of OCT imaging

Within the retina, retinal ganglion cell axons are unmyelinated until they pass through the lamia cribosa. Therefore, RNFL imaging has the unique advantage of measuring the thickness of axonal and other retinal structures that can ultimately be used in assessing neurodegeneration and potentially neurorepair. OCT is similar to B-mode ultrasound B-mode imaging, but uses light instead of sound to form images. An optical beam is scanned along the retina and the machine measures echo-time delays in order to synthesize a picture of the retinal structure (Jindahra et al., 2010; Lameril et al., 2009; Sakata et al., 2009; Glisson and Galetta, 2009). Advances in OCT, including the development of spectral- (Fourier) domain technology, provide increased sensitivity and capacity for careful analysis of pathologic changes in the retina in vivo. Representative group data for OCT in patients with MS and disease-free controls are presented in Table 1. Time-domain (TD) OCT (first generation widely studied in MS) shows substantial differenes in RNFL thickness between eyes of patients with MS and disease-free controls (95.5$\pm$14.5 μm vs. 104.5$\pm$10.7 μm) MS eyes with a history of ON have even greater degrees of thinning on average (85.7$\pm$19.0 μm). For spectral-domain (SD) OCT techniques, there are differences in scaling from TD OCT, leading to smaller absolute differences in RNFL thickness (92.9$\pm$10.0 μm for controls vs. 87.6$\pm$11.1 μm in MS eyes without a history of ON). Larger studies will further refine the precision of these representative average values. Statistically combined data for studies of TD OCT as of 2009 are presented in a meta-analysis that highlights $>$96 articles, with analyzable data from 36 studies of OCT in MS (Petzold et al., 2010).

An advantage of OCT is that it demonstrates high degrees of both inter-rater and test-retest reliability for TD and SD techniques (Cettomai et al., 2008). In fact, recent studies of SD OCT show that this newer technology produces measurements that are more reproducible than TD OCT (Syc et al., 2010). A study of 58 patients and 38 controls found that intraclass correlation coefficients (ICCs) ranged from 0.92 to 0.97 for inter-visit, 0.83–0.99 for intra-rater, and 0.94–0.99 for inter-rater reproducibility. Given its high degrees of reliability, sensitivity and ease of use (pupillary dilation not usually needed), OCT is an ideal method for assessing pathologic changes in the visual pathway of patients with MS. As such, these techniques have been included in most recent MS clinical trials, and are now considered essential for evaluating new therapies for acute ON.

3.3. OCT investigations in MS and optic neuritis (ON)

During the course of their disease, between 30 and 70% of MS patients will have acute ON (Balcer, 2006; Frohman et al., 2005). Since patients with acute demyelinating ON typically have overt, subacute symptoms of pain on eye movement, visual acuity loss, color desaturation, and visual field abnormalities, followed by substantial RNFL axonal loss by OCT (20–40 μm on average), ON is an ideal model for studying neuroprotective and neurorepair agents in MS.

In 1999, OCT was first utilized in a study by Parisi et al. to investigate a group of patients who had a history of ON with complete recovery of visual acuity. When compared with control eyes, RNFL thickness was found to be 46% worse in the eyes affected by acute ON. The affected eyes were also found to have RNFL thickness 28% worse when compared to the unaffected eyes of the same patient ($P<0.01$) (Parisi et al., 1999). A subsequent investigation by Trip et al. (2005) substantiated these findings among eyes of patients with a history of ON and incomplete recovery. This cohort of 25 patients with a history of unilateral ON found that ON eyes had a 33% reduction in RNFL thickness of patient eyes compared to disease-free control eyes ($P<0.001$) (Trip et al., 2005). These authors also reported reductions in total macular volume in ON eyes compared with controls ($P<0.001$), and also showed differences and between affected and unaffected eyes of patients in the study ($P<0.001$).

A more recent study by Costello et al. showed that close to 75% MS patients with ON will have RNFL losses between 10 and 40 μm in their affected eyes within 3 and 6 months following the acute event. Considering that the average RNFL thickness by TD OCT in disease-free controls is ~105 μm (92 μm in MS eyes), and that healthy control eyes lose only 0.017% of total RNFL thickness annually, the RNFL thinning associated with acute ON is substantial and provides a target for reduction of axonal loss in future clinical trials of ON (Syc et al., 2010; Galetta et al., 2011). Costello et al. also established a threshold value of 75 μm by TD OCT, below which there was a corresponding decline in visual function by computerized static perimetry visual field mean deviation (Costello et al., 2006). Among eyes in a collaborative heterogeneous cohort of patients with MS, eyes with a history of ON appear to have a threshold of approximately 80 μm by TD OCT, below which they show sustained abnormalities by low-contrast letter acuity.

Trials of neuroprotective or repair agents for ON will also likely establish a "therapeutic window," or time frame within which the agent should ideally be given in order to maximize the effect of preventing axonal/ neuronal loss. A recent study used several tests, including high-contrast VA and low contrast visual acuity, Farnsworth-Munsell 100 Hue color testing, automated visual fields, pattern VEP and RNFL thickness by TD-OCT in order to investigate when changes occurred in the course of ON (Henderson et al., 2010). This study determined that after a mean of 4.75 months follow-up, 99% of the total amount of RNFL axonal loss that was measured from baseline had occurred. After 1.65 months (95% CI, 0.96–2.32; $P<0.05$), RNFL thinning could be observed when compared to the unaffected fellow eye. Worse recovery was associated with more significant RNFL decline over three months of observation ($P=0.002$). Significant macular volume loss between initial assessment and follow-up was also established (Henderson et al., 2010).

ON is thus a predictable cause of axonal and neuronal degeneration in the eyes of patients with MS. Interestingly, recent reports have shown that regardless of a history of ON, RNFL thinning can be seen in heterogeneous MS cohorts. Low-contrast letter acuity loss is also associated with RNFL thinning in MS eyes without a history of ON (Fisher et al., 2006). In a cross-sectional study of 90 patients and 36 disease-free controls, RNFL thickness was reduced in the eyes of patients without a history of ON (105 μm; $P=0.03$). This study also showed that both MS eyes with a history of ON and MS eyes without a history of ON had significant damage as compared with disease-free controls (Fisher et al., 2006). There was a loss of 4 μm of RNFL thickness for every one line of low-contrast letter acuity loss among eyes of MS patients. RNFL thickness was associated with overall degrees of neurologic impairment, worse EDSS scores and longer disease duration.

Studies have shown that RNFL thickness becomes reduced over time in MS regardless of the history of ON (Talman et al., 2010). MS patients and controls at three academic centers underwent OCT imaging and visual testing. In patients without a history of ON, an average RNFL thickness of MS eyes were reduced by 2.9 μm after 2–3 years and by 6.1 μm after 3–4.5 years ($P<0.001$). This data would indicate a significant need for monitoring the structural changes even in eyes without a history of ON.

4. Current research in MS

Using GDx-VCC, a type of scanning laser polarimetry, our group has demonstrated that RNFL thinning is related to visual loss. While OCT RNFL thickness is reflective of structural changes in the ganglion cell axons, measurement of the RNFL by scanning laser polarimetry (GDx) can demonstrate underlying microtubule integrity based on the property of birefringence. (Zaveri et al., 2008). This technique is particularly valuable in the setting of MS because it is able to quantify integrity of the RNFL in the setting of optic disc edema (common in acute ON) (Banks et al., 2003).

OCT and GDx measurements of RNFL have similar associations with visual loss, particularly in eyes with a history of acute ON (Zaveri et al., 2008). Uniquely, GDx is able to detect changes in small specific areas within the retina. GDx may ultimately be used to evaluate patients in clinical practice who are experiencing acute ON, particularly since OCT may be less valuable in the setting of acute optic disc edema.

OCT has shown advancements in recent years which will improve reproducibility and allow for better image quality. Newer high-resolution SD OCT has features which make scan-to scan variability and image quality better. Automated disc-centering and longitudinal co-registration reduces scan-to-scan variability. Correction for eye movement allows greater ease and improved image quality in patients with difficulty focusing their eyes. The new OCT scanners are faster, have greater resolution and can image more of the retina.

With the development of SD- OCT, segmentation of the layers of the retina has been made possible. This is important advance since neuronal loss is regarded as a correlate of MS disability (Fisher et al., 2008; Pirko et al., 2007; Fisniku et al., 2008; Shiee et al., 2010; Filippi et al., 2010; Pitt et al., 2010). Studies using TD-OCT had shown decreased total macular volume in MS patients and this measure could estimate ganglion cell neuronal loss (Burkholder et al., 2009). Now, SD-OCT has provided the first opportunity to more directly estimate thinning of the GCL+IPL through manual segmentation (Davies et al., 2011). In a pilot study, Davies et al., showed the eyes of patients with MS (n=16) had significantly lower GCL volume as compared with controls ($P<0.001$). There was not a significant association between GCL and high-contrast visual acuity loss, and low-contrast acuity correlated with GCL volume scores (P=0.003).

Given the amount of time required to segment retinal layers manually (approximately 2 h), there is a need for computerized algorithms that allow for measurement of the retinal layers on a large scale. Studies of glaucoma had successfully used computerized segmentation algorithms to quantify the layers of the retina and these methods have now been applied to SD OCT images of eyes of MS patients (Tan et al., 2009; Ishikawa et al., 2005).

OCT measurements of RNFL thickness and other parameters can also differ among MS subtypes. Patients with secondary progressive MS (SPMS) have greater reductions in RNFL thickness (83.4 μm by TD OCT) compared to patients with clinically isolated syndrome (CIS) (101.2 μm, P=0.0009) and relapsing remitting MS (RRMS) (103.7 μm, P=0.001) (Costello et al., 2010). In eyes with a history of ON, patients with SPMS had greater thinning (39.5 μm at follow-up) than in CIS (58.1 μm, P=0.03) or RRMS (48.2 μm). From these data Costello et al. (2010) concluded that RNFL thickness is likely ton represent structural changes that are related to disease subtype.

Benign MS is another area in which definitions and diagnostic criteria may unintentionally minimize the apparent role of visual pathway disease. Patients with benign MS most typically have an EDSS $\leq$3 and $\geq$15 years disease duration, and are therefore thought to follow a milder course when compared to those with typical RRMS (Galetta et al., 2012). Our group recently conducted a longitudinal analysis of EDSS scores, visual function, OCT measurements, and QOL assessments in a subset of patients with benign MS. RNFL thickness was measured using TD OCT, QOL scales included the NEI-VFQ-25 and SF-36. Using the most common benign MS definition of EDSS $\leq$3 and $\geq$15-year disease duration, 13 patients (26 eyes) met critieria. Despite the relatively lower EDSS score, patients with benign MS had similar if not greater degrees of RNFL thinning from baseline during an average follow-up of 1.6 years (benign MS eyes-3.6 μm, P=0.0008 vs. baseline, paired t-test; typical MS eyes -3.3 μm, $P<0.0001$). Vision-specific QOL scores were likewise worse among patients with benign MS compared to those with typical RRMS (NEI-VFQ-25 composite scores 75$\pm$21 vs. 88$\pm$11, P=0.005, accounting for age) and history of ON distinguished between the two (need to clarify what this means) (P=0.002). These data provide further evidence that the EDSS does not adequately capture visual pathway axonal loss and visual impairment, both of which are likely contributors to disabiltiy in patients with benign MS.

Patients with the macular thinning predominant (MTP) phenotype of MS are of interest to our understanding of gray matter/ neuronal loss as manifested in the retina. Saidha et al. (2011) examined a cohort of patients with normal peripapillary RNFL thickness but thinning of the macular region to the 5th percentile or less using SD OCT. While this group had thinning of the outer retinal layers ($P<0.001$ for inner and outer nuclear layers), they showed little thinning of the GCL layer, suggesting a unique pattern of retinal neuronal cell loss in patients with this phenotype.

Pathologic studies of postmortem eyes of patients with MS (n=82) have shown GCL loss in 79% (68). Using algorithms originally designed for investigation of GCL+IPL thinning in glaucoma and developed at the University of Pittsburgh, our collaborative research group has investigated in vivo measurement of the GCL+IPL and other retinal layers in MS. In a study of 122 patients (239 eyes) and 31 controls (61 eyes), macular RNFL ($P<0.001$) and GCL+IPL (P=0.001) was significantly thinner in MS eyes, accounting for age and within-patient, inter-eye correlations). Macular RNFL thickness and GCL+IPL were also found to be significantly thinner in MS eyes with a history of ON (P=0.001). GCL +IPL and macular RNFL ($P<0.001$ and P=0.006) were the retinal layers that were most strongly associated with reduced vision-specific QOL scores (NEI-VFQ-25 and 10-Item supplement composite) (Fig. 3). Ganglion cell layer neuronal loss in MS is likely to be an important indicator visual pathway disease in MS.

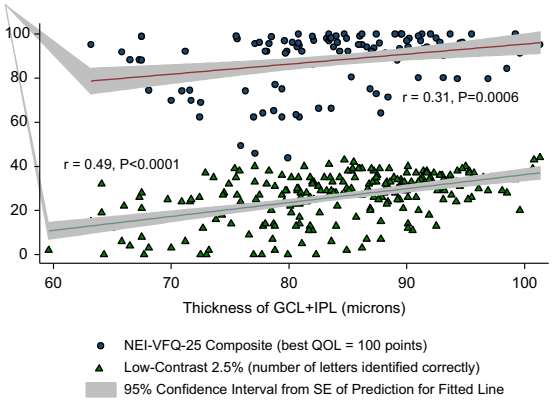

Fig. 3 Scatter plot and fitted linear regression line showing relation of ganglion cell layer plus inner plexiform layer (GCL+IPL) thickness to 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) composite scores and low-contrast acuity at 2.5% level. The regression lines represent fitted values for mean GCL+IPL thickness for each value of NEI-VFQ-25 or low-contrast acuity; the gray shaded areas show the 95% confidence intervals from the standard errors of the predictions for the fitted lines. This graph for all multiple sclerosis eyes illustrates that there are very few outliers with respect to quality of life (QOL) or low-contrast acuity. Linear correlations were significant. Accounting for age and adjusting for within-patient, intereye correlations, the relation of QOL and low-contrast acuity to GCL+IPL thickness was significant ($P<0.001$, generalized estimating equation models). Reprinted with permission from: Walter et al., 2012.

5. Future directions

There are a wide variety of OCT instruments currently available to access patient outcomes. Unfortunately, there are no standard protocols between the different machines, and it is difficult to meaningfully understand how values ascertained from different machines relate to each other. Each machine uses its own methods for analysis and has its own protocol. The capacity of OCT to measure axonal and neuronal degeneration is critical as we increasingly appreciate vision as a model for disease in MS.

New research should focus on establishing the spatial and temporal relationship between axonal injury and ganglion cell loss. This will be helpful in further advancing our ability to act most appropriately within the disease course of MS patients.

6. Conclusion

Axonal and neuronal loss are important markers of disease in MS. Through the use of low-contrast letter acuity and OCT, the structure–function correlations afforded by the anterior visual pathway can serve as a model for testing new MS therapies, particularly those involving neuroprotection and repair. Application of group data from vision research studies and trials in MS to individual patients will be best achieved by clinical use of the visual, OCT, and QOL measures. This will not only develop more extensive data from the clinical setting, but will provide perspective to MS providers regarding the expected ranges of values for patients with and without a history of acute ON.

Disclosure statements

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Conflict of interest statement

The authors declare no conflict of interest

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