OCT and Multiple Sclerosis

11

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11.1 Background

Multiple sclerosis (MS) is a highly heterogeneous autoimmune neurological disorder characterized by inflammation, demyelination, and neuroaxonal degeneration within the central nervous system (CNS), and the leading cause of neurological disability among young adults worldwide [1]. The precise aetiology remains unknown and may be multifactorial, with a range of environmental factors appearing to act against the background of a complex polygenetic trait [2]. It is believed that, initially, the disease is predominantly driven by aberrant peripheral immune cells, including T- and B-cells, that, upon (re)activation, target CNS myelin antigens [2]. MS frequently manifests with an initial inflammatory and demyelinating event affecting the CNS, termed clinically isolated syndrome (CIS) [3]. Current diagnostic criteria require evidence of clinical or radiological disease activity dissemination in both time and space, and allow a diagnosis of MS to be made based on a single clinical event when confirmed by radiological evidence of previous disease activity [4]. Relapsing-remitting MS (RRMS) is the most common form of the disease and is characterised by clinical episodes of inflammatory demyelination ('relapses') followed by periods of variable recovery and relatively stable neurological status ('remissions') [3, 4]. Patients initially diagnosed with RRMS may develop a gradual, progressive accumulation of disability independently of relapses, defined as secondary progressive MS (SPMS); alternatively, a minority of patients may exhibit progressive disease activity in the absence of relapses from disease onset, defined as primary progressive MS (PPMS) [3, 4]. In addition to these phenotypical classifications, MS may also be described as clinically or radiologically active, with or without evidence of disease progression [3].

Despite a highly heterogeneous clinical presentation and disease course, involvement of the visual system is a near-ubiquitous hallmark of the disease [5, 6]. In the afferent visual pathway, optic neuritis (ON; an acute or subacute inflammation of the optic nerve) is the most common manifestation of MS [7]. ON may occur within the context of previously-diagnosed MS, or as an initial clinical event strongly suggestive of MS but not immediately fulfilling diagnostic criteria for the disease [4] (CIS). It should be noted that ON may also occur idiopathically, in systemic disease, and in immunological conditions other than MS [8]; however, for the purpose of this overview, the nomenclature ON should be understood to refer only to that associated with MS and CIS. This prevalence of anterior visual pathway involvement, the accessibility of the retina for viewing retinal neurons and their axons *in vivo*, and the unmyelinated nature of ganglion cell axons within the retina (unique within the CNS), have ensured that the anterior visual pathway has generated considerable interest as a model for research in MS [9]. Much of this interest has been facilitated by the development of optical coherence tomography (OCT) and its increasing use in neurological clinics.

Since the first retinal OCT scans were acquired in 1991 [10], the introduction of spectral-domain OCT (SD-OCT), offering higher resolution and acquisition speed than previous time-domain OCT (TD-OCT) technology, has permitted the development of automated or semi-automated software algorithms enabling the definition

and delineation of the boundaries separating the retinal layers (Fig. 11.1), in addition to coarse measures of retinal thickness such as total macular volume (TMV). These layers and complexes include the retinal nerve fibre layer (RNFL), which is most commonly measured around the optic nerve head (pRNFL) but may also be measured at the central macular region (mRNFL); the ganglion cell layer (GCL); inner plexiform layer (IPL); the inner nuclear layer (INL); the outer plexiform layer (OPL); the outer nuclear layer (ONL); and the photoreceptor layer (PRL). As the boundary between GCL and IPL may be difficult to visualise and accurately define, these layers are typically combined and described as the ganglion cell and inner plexiform layer (GCIP or GCIPL are equally acceptable abbreviations [11];

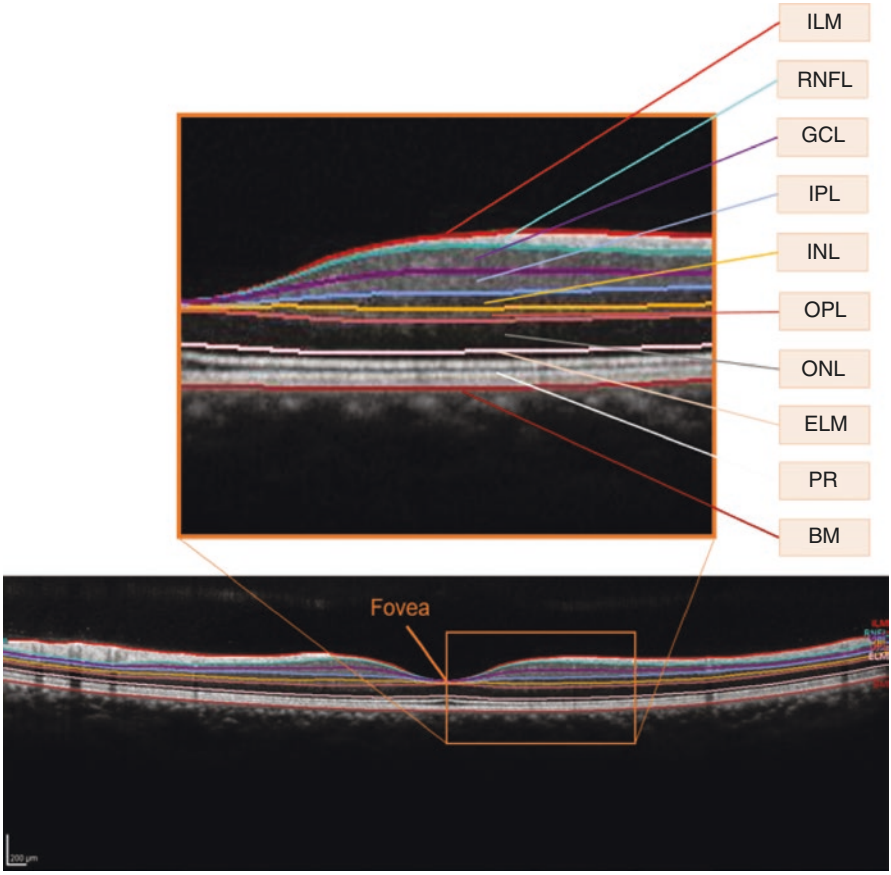

Fig. 11.1 Segmented macular OCT B-scan of a healthy individual, showing the delineation of the retinal layers. *ILM* inner limiting membrane, *RNFL* retinal nerve fibre layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer, *INL* inner nuclear layer, *OPL* outer plexiform layer, *ONL* outer nuclear layer, *ELM* external limiting membrane, *PRL* photoreceptor layers, *BM* Bruch's membrane. Note that GCL and IPL are typically aggregated to form the ganglion cell and inner plexiform layer (GCIP), and other layers may also be aggregated, depending on the segmentation software used and/or aims of individual studies

throughout this work, GCIP will be used for consistency). However, different proprietary software algorithms and studies may choose to additionally aggregate or otherwise classify layers of the retina (e.g., INL-OPL; outer retinal layers, ORL; ganglion cell complex, GCC). Whichever approach individual laboratories or researchers choose when conducting OCT research in MS patients, transparent and precise definition of the relevant retinal structures is vital [11]. This process of retinal layer delineation, referred to as segmentation, has led to a large and growing body of literature examining the structure of the full range of retinal layers and complexes in the eyes of patients with MS.

Image quality is paramount for accurate and reliable definition and verification of the intra-retinal boundaries, and early recognition of this fact by MS researchers led to the development of the first OCT quality guidelines validated for use in MS research, the OSCAR-IB consensus criteria [12]. These guidelines emphasise the importance of signal strength, scan centration, algorithm performance (i.e., errors of automated segmentation), absence of co-existing retinal pathology (which may affect OCT interpretation), fundus illumination, beam placement, and exclusion of any other obvious acquisition errors when assessing OCT data. Application of the OSCAR-IB criteria has been shown to result in high inter-rater agreement regarding the acceptance or rejection of scans in multi-centre studies [12, 13], and may thus maximise the reproducibility of OCT studies. Recent work analysing the reliability of inter-rater, multi-centre manual correction of automatically segmented OCT scans, utilising the OSCAR-IB criteria, recorded excellent agreement between raters, in particular for the inner retinal layers [14]. The agreement between raters appeared to be greater than in previous work predating the OSCAR-IB criteria [15]. We therefore recommend adherence to the OSCAR-IB criteria at all times when evaluating OCT scans, and to the APOSTEL recommendations for describing OCT scan protocols and analyses [11] (described in detail in Chap. 3), whenever publishing results of OCT studies in MS patients. We also recommend that all OCT scans for any study are segmented using identical software, as different versions of the same proprietary software have been shown to produce small but significant differences in axonal thickness in patients with MS and in control subjects [16].

11.2 OCT Findings in Patients with MS

Findings to date consistently show that pRNFL thickness is reduced in the eyes of MS patients without previous ON relative to healthy control subjects [17–25] (Fig. 11.2), although this may not necessarily be the case in patients with CIS [26] or newly diagnosed MS [27]. Meta-analyses have quantified this loss of thickness in MS patients as being on average just over 7 μm whether measured with SD-OCT or TD-OCT technology [28, 29]. Thickness of the temporal quadrant of pRNFL has been suggested to be preferentially affected by MS [23], although other studies failed to observe this pattern in eyes without previous ON [21]. Likewise, sparing of the nasal quadrant has been proposed [23] but not confirmed [21]. Some of these differences may be attributable to subtly different RNFL quantifications obtained by

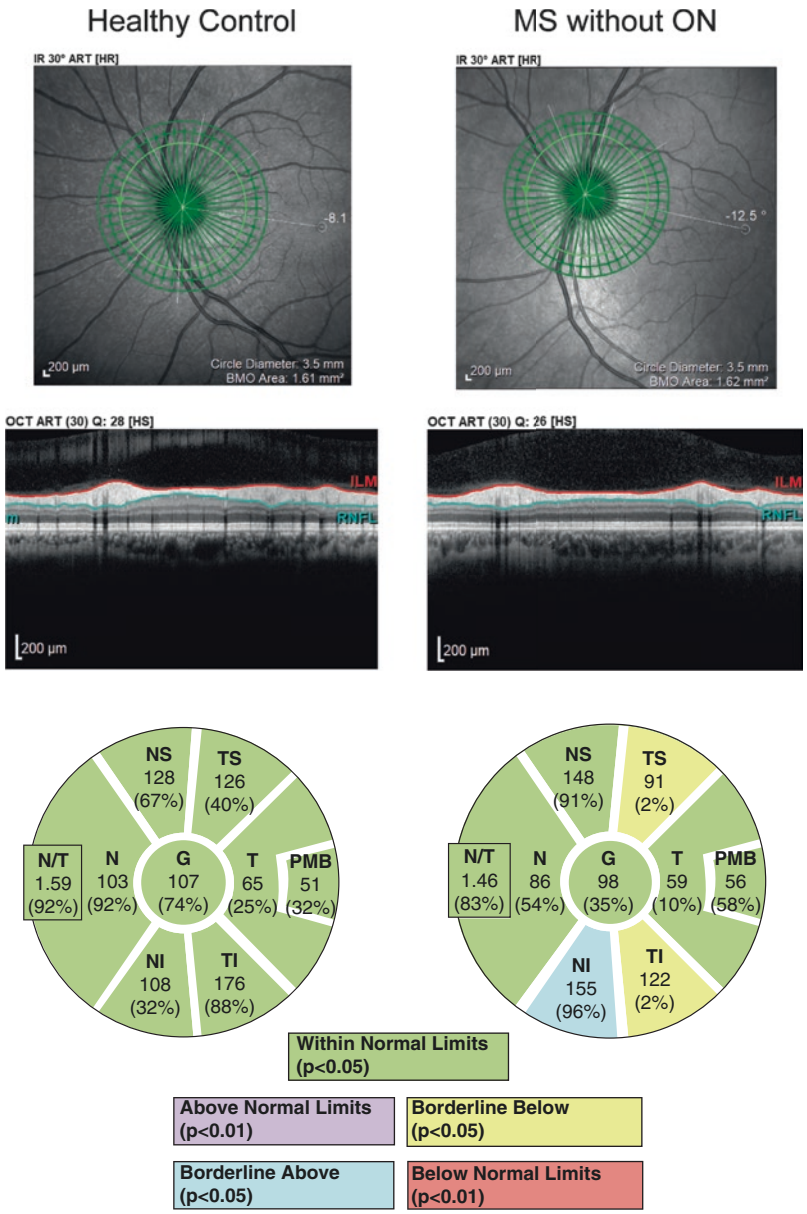

Fig. 11.2 pRNFL analysis from the left eyes of a healthy individual and a multiple sclerosis (MS) patient without previous optic neuritis (ON), obtained from a Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany). The global averaged (G) thickness is reduced in the patient with MS, as are the thicknesses of the majority of the individual sectors; in the case of the temporal superior (TS) and temporal inferior (TI) sectors, thickness is below the 95th percentile of age-matched normal values and so is classified as borderline below average (and colour-coded yellow) by the proprietary software. The borderline above average thickness in the nasal inferior (NI) sector in the MS patient is an artefact caused by a retinal blood vessel

different OCT devices [30]. Longitudinal studies of RNFL atrophy show that MS eyes without a history of ON undergo an average decline in RNFL thickness of between 0.5–1.5 μm per year [31–33], approximately 3–10 times faster than healthy control subjects. This rate of decline is highest in the early stages of the disease (up to approximately 10 years of disease duration) and thereafter declines, consistent with a plateau effect [31]. The inverse relationship between RNFL atrophy rate and disease duration (Fig. 11.3) may explain the different annual RNFL loss rates obtained in different studies in cohorts with varying average disease duration, and should thus be considered when planning and evaluating future research.

MRNFL has also been shown to be thinned in MS patients [18, 19, 26], but by an average of just over 2 μm relative to normal individuals [28]; therefore it appears that pRNFL may offer more power than mRNFL when investigating axonal integrity in MS patients, and offers the additional advantages of being quicker to measure and requiring less post-hoc correction (typically one B-scan rather than, e.g., 19). Additionally, as an outcome measure mRNFL has been suggested to be less reliable than pRNFL due to the density of vascular perfusion between the fovea and optic nerve head potentially causing artefact-based segmentation errors [34]. These factors, combined with the relatively recent development of macular segmentation algorithms compared to software able to reliably quantify pRNFL, have ensured that pRNFL remains the more widely studied outcome measure in MS research.

In addition to the RNFL, thickness of the GCIP is also reduced in the eyes of MS and CIS patients without previous ON [17–19, 24–27, 35–37], by an average of 6.3 μm relative to control subjects [28]. Using the 1, 2.22, and 3.45 mm Early Treatment Diabetic Retinopathy Study (ETDRS) grid centred on the fovea, it was shown that average GCIP thickness declined by 0.9 μm over 2 years in MS patients without previous ON, a rate of loss approximately double that observed in healthy individuals [31]. As with the RNFL, annual rates of GCIP loss appear to be inversely related to disease duration (Fig. 11.3) [31]. A similar study also found that MS patients lost GCIP thickness just over twice as fast as control subjects [32], although quantitative rates of GCIP loss cannot be compared between the two studies due to different OCT devices, acquisition protocols, and retinal areas analysed.

In contrast to the RNFL and GCIP of the inner retina, INL thickness in MS patients seems to not differ significantly from that of control subjects [17, 18, 37, 38] and appears to remain stable in the eyes of MS patients without ON irrespective of disease duration (Fig. 11.3), at least over a 2 year period [31]. However, disease activity, treatment status, and (indirectly) disease duration may influence these results [24]. Rather than being a marker for neurodegeneration like the inner retina, the INL currently holds promise as a biomarker for inflammatory disease activity and response to disease-modifying therapy in MS. OCT thus has the potential to objectively capture and quantify the two main hallmarks of MS disease activity, neuronal degeneration and inflammation. A detailed discussion of the potential role of the INL in MS research can be found in Sect. 11.5.

Studies of the structure of the retina distal to INL are relatively sparse at the time of writing, and interpretation is made more challenging by the fact that some studies aggregate two or more of the retinal layers for analyses (e.g., INL and OPL [19];

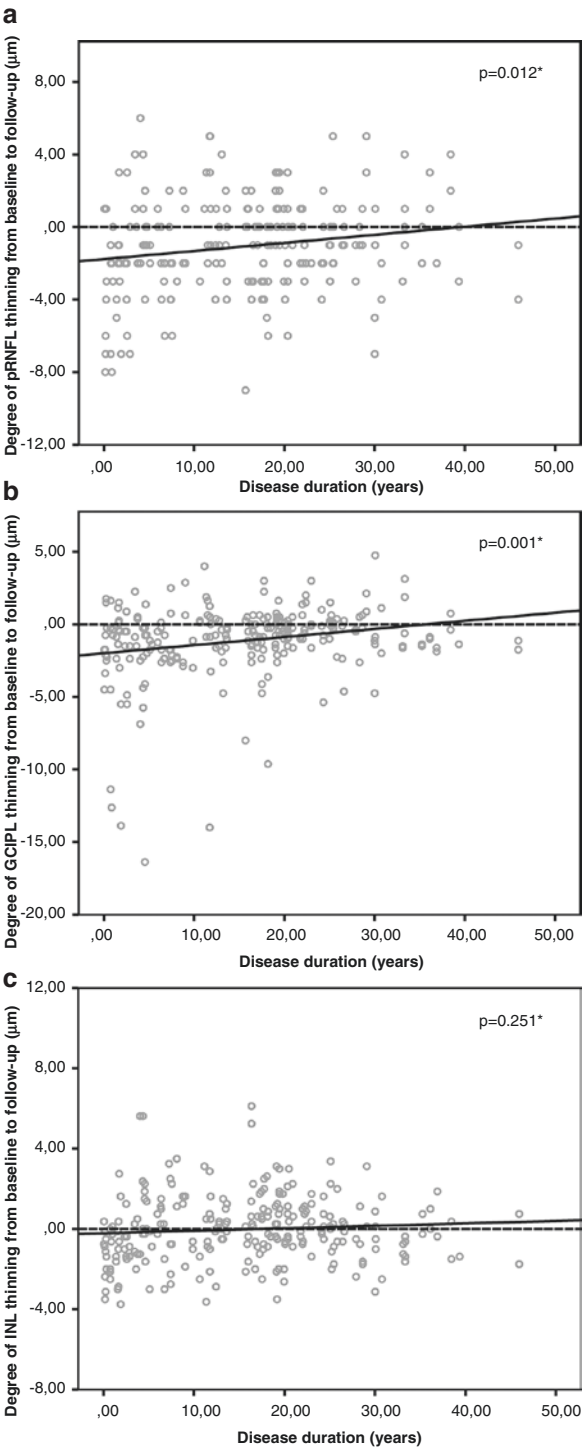

Fig. 11.3 Scatter plots showing the degree of thinning of the peripapillary retinal nerve fibre layer (pRNFL, **a**), ganglion cell and inner plexiform layer (GCIP; here GCIPL, **b**), and inner nuclear layer (INL, **c**) over a 2 year period in patients with multiple sclerosis (MS). RNFL and GCIP loss was greater in patients with a lower disease duration, whilst INL remained approximately constant over the study period irrespective of disease duration. Reproduced from Balk et al. Journal of Neurology 263, 1323–1331 (2016) under the terms of the Creative Commons CC BY license

ONL and PRL [36]). However, published studies to date have consistently found no effects of MS on the thickness of the retinal layers distal to INL [18, 19, 24, 25, 39].

Although the majority of patients with MS exhibit a relapsing-remitting disease course (RRMS), and thus the majority of the studies above relate mainly to RRMS and CIS patients, researchers have also measured differences in OCT parameters between the different MS phenotypes. Patients with progressive forms of MS (PPMS; SPMS) show reduced RNFL thickness compared to patients with RRMS [20, 40] and healthy control subjects [25, 40, 41]. As would be expected, GCIP is similarly reduced [25, 40, 41]. INL, but not ONL, is also thinned in patients with progressive forms of MS relative to control subjects [25, 40]. Findings with regard to the OPL in progressive MS are not unanimous [25, 40], whilst PRL thickness has been reported to be thinner in patients with progressive MS relative to control subjects but comparable to that of patients with RRMS [40].

Due to the historical lack of medical therapy for patients with PPMS (thereby reducing the need for frequent clinic visits to monitor effectiveness and side-effects of treatment) and the relative rarity of this phenotype relative to RRMS and CIS, PPMS patients are arguably underrepresented in OCT studies and, when included, it may only be possible to recruit a relative small cohort in single centre studies (e.g., 12 PPMS patients [25]). Such difficulties are likely to have the effect of decreasing the potential statistical power in studies of PPMS. This situation may improve in the future, following the recent licensing of ocrelizumab (Ocrevus®), a monoclonal antibody targeting the CD20 antigen expressed on B-cells and (to a lesser extent) T-cells, as the first treatment for use in patients with PPMS. This may lead to an increase the numbers of PPMS patients regularly attending neurology clinics for reasons of efficacy and safety monitoring.

It has been proposed that OCT may be used to define novel MS phenotypes defined by primary retinal pathology (i.e., structural and/or functional changes unrelated to a history of ON) [42]. These authors documented a subset of their MS cohort who exhibited thinning of the macula in the presence of normal RNFL thickness relative to normative data, with segmentation revealing thinning of both the INL and ONL, a phenotype the authors named “macular thinning predominant” (MTP) [42]. No MTP eyes had a prior history of ON, and no significant differences in INL or ONL thickness were observed between non-MTP MS patients and healthy controls [42]. Clinically, MTP-MS patients were found to have reduced high- and low-contrast visual acuity (HCVA; LCVA) and higher Expanded Disability Status Scale (EDSS; the most widely accepted and most broadly applied measure of clinical disability in MS patients) scores when compared to non-MTP MS patients [42]. Subsequent works were unable to confirm the existence of a distinct subset of MS patients consistent with the proposed MTP phenotype [19, 43] and found INL thinning in the absence of ONL changes only in patients with PPMS [25]. Differences in OCT hardware, software, and manufacturer-specific normative databases, as well as in patient populations, doubtless contribute to this apparent dichotomy. However, functional evidence consistent with similarly ON-independent abnormalities of the retinal layers distal to GCIP in patients with MS has been credibly reported by a number of authors working independently [35, 39, 44–47], and INL atrophy in MS eyes has been histologically confirmed post-mortem [48].

In MS, patients of African-American ethnicity have been shown to accumulate disability more rapidly [49, 50], and exhibit more cerebellar dysfunction [49], compared to Americans of Caucasian ethnicity; they are also more likely to have PPMS and less likely to have RRMS [49]. Using OCT, it has also been found that African-American MS patients have thinner RNFL (in the temporal quadrant only) and GCIP, which decline in thickness more rapidly, than Caucasian Americans [51, 52]. Thus, OCT results appear to be consistent with a more neurodegenerative phenotype in African-Americans [51].

Fingolimod (Gilenya®) is a modulator of sphingosine 1-phosphate receptors prescribed as an immunomodulatory therapy in MS. Whilst its high efficacy [53, 54] and oral administration are attractive, a small number of patients (up to 1% of treated RRMS patients [55, 56]) develop cystoid macula oedema (CMO; an accumulation of fluid in the central retina most likely consequent to breakdown of the blood-retinal barrier [57]) as a side-effect of the treatment (Fig. 11.4). It is therefore recommended that patients undergo ophthalmological examination before commencing therapy, and again 3–4 months afterwards, a time interval in which the

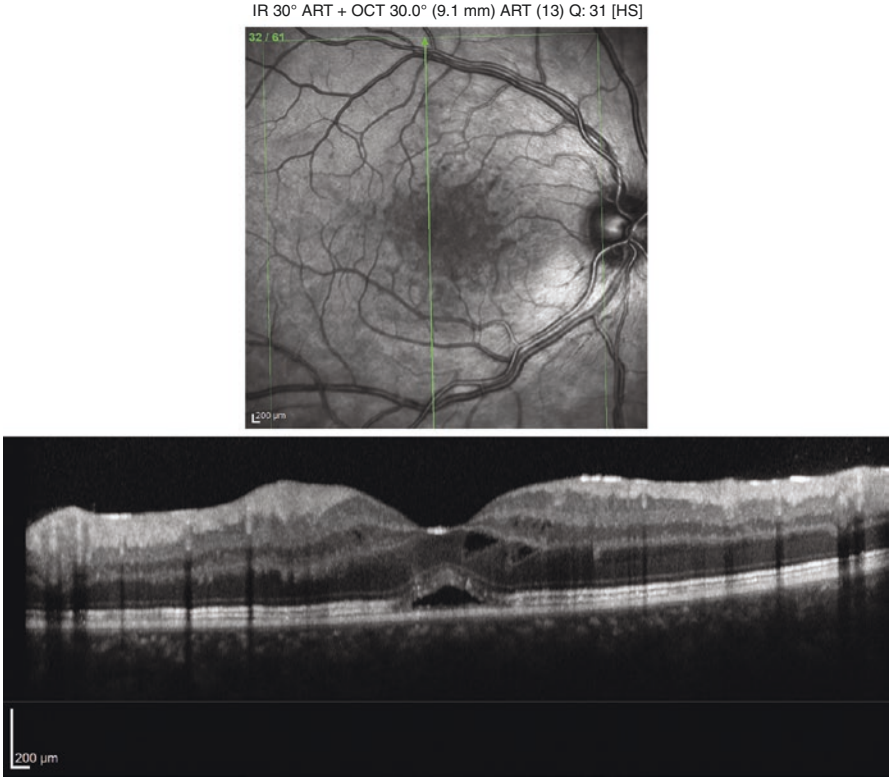

Fig. 11.4 OCT scan of the right eye of a patient with multiple sclerosis (MS) who has developed cystoid macula oedema (CMO) consequent to medical treatment with fingolimod (Gilenya®). Cystoid spaces are visible in the outer and (to a lesser extent) inner nuclear layers, as well as a small subfoveal accumulation of subretinal fluid

majority of CMO cases manifest [58]. OCT has been demonstrated to be significantly more sensitive than fundoscopy in detecting CMO [59], and therefore is of utility when assessing and monitoring MS patients undergoing treatment with fingolimod.

Recent developments in OCT technology have led to the development of OCT angiography (OCT-A), which is able to evaluate both arterial and venous density at the retina and optic nerve head down to the capillary level (OCT-A is described in detail in Chap. 4). Retinal vascular abnormalities such as periphlebitis have long been known to exist in some patients with MS [23, 60], but precise examination and quantification of the vessels with OCT was not possible until the introduction of OCT-A. Perfusion of the optic nerve head (as quantified by the density of visible vessels) has been shown to be reduced in MS eyes without previous ON compared to control subjects [61]. Results regarding macular perfusion are mixed at the time of writing, with a single study showing reduced vessel density in MS patients without ON [62] but other studies recording no differences with healthy control subjects [63, 64]. Increased vessel density in the choriocapillaris may be associated with prospective disease activity in MS [64], via an as-yet unknown mechanism. Future OCT-A studies are vital in order to elucidate the precise role of the retinal and choroidal vessels in MS.

11.3 OCT Findings in Patients with Optic Neuritis (ON)

ON is the most frequent manifestation of anterior visual pathway involvement in MS [7], being the first clinical sign of CIS in over a fifth of patients [8], and post-mortem evidence of pathological changes to the optic nerve has been documented in up to 86% of MS eyes [48, 65]. Clinically confirmed episodes of ON occur in approximately 70% of MS patients during their disease course, typically during the relapsing-remitting phase [8]. Although presentation is variable, symptoms of ON commonly include reduced vision, periocular or retrobulbar pain (which typically worsens upon eye movements), and altered colour perception [66, 67]. Visual phenomena such as scintillations and/or phosphenes may also be reported [67]. Clinical signs upon examination may include reduced high- and/or low-contrast visual acuity (HCVA; LCVA), a relative afferent pupillary defect (RAPD), perimetric abnormalities (central scotoma [68], centrocecal scotoma, paracentral scotoma, or diffusely reduced sensitivity [69]), and abnormalities on colour vision testing [66] (although note that MS patients without previous ON may display similar abnormalities of colour vision [70]). Swelling of the optic nerve head is visible on fundoscopy in approximately one third of patients [66], with the remainder presenting with a normal fundus appearance due to inflammation being confined to the retrobulbar portion of the optic nerve and not extending to the optic nerve head. Visual function typically recovers spontaneously over a period of weeks to months [71], however many patients experience persistent visual impairment such as reduced LCVA and residual impairment of colour vision perception, with corresponding measures of

vision-related quality of life being reduced [72]. The Pulfrich phenomenon, caused by inter-ocular differences in afferent conduction velocity consequent to unilateral demyelination, may be noticed by patients during the recovery phase [67]. These visual findings may be recorded even when HCVA returns to normal or near-normal levels [22, 73, 74]. Treatment with corticosteroids may accelerate clinical recovery after ON [75] and reduce the risk of progression to MS over approximately 2 years [76], but has minimal effect on visual outcome [75, 76]. Given these factors, and the fact that MS patients have been shown to rate vision as their most important bodily function irrespective of disease duration and disability [77], it is clear that ON is of vital importance in the study of MS. Retinal injury is currently believed to occur following inflammatory demyelination and axonal damage of the optic nerve by a process of retrograde degeneration toward the retinal ganglion cells [78].

OCT examination of MS or CIS patients with a history of ON almost invariably reveals reduced pRNFL [18–20, 28, 29, 34, 36, 38, 39, 79–84]. Meta-analyses have quantified this loss of pRNFL as an average of just over 20 μm relative to healthy control subjects both with SD-OCT and TD-OCT [28, 29]. Considerable inter-individual variation has been documented [83], most likely reflecting the heterogeneity both of clinical outcomes after ON and in MS generally. However, this figure of 20 μm refers to the pRNFL averaged over 360° around the optic nerve head; when the superior, inferior, temporal and nasal quadrants are compared, the temporal quadrant may be the most sensitive in visualising and quantifying axonal loss after ON [21, 80, 85–88]. Thickness of the pRNFL in the papillomacular bundle (PMB), comprised of axons from the foveal region and the area between the fovea and optic nerve head which are anatomically distinct from the predominating arcuate organisation of RNFL axons, has been reported to be the most sensitive individual OCT parameter in blinded detection of previous ON despite its inclusion not increasing the overall sensitivity of such analyses [86]. Preferential involvement of the temporal and PMB RNFL would be consistent with the reported predominance of central and centrocecal visual field defects in ON [68, 69]. Thickness of the superior and inferior quadrants is also significantly reduced after ON in MS patients [23, 80, 85, 89], whilst the balance of evidence to date suggests that the nasal quadrant is relatively unaffected [23, 80, 85, 86, 89]. Loss of pRNFL appears to have plateaued by approximately 6–12 months after the first symptoms of ON [80, 82, 83]. An inter-ocular pRNFL thickness difference of more than 5–6 μm is strongly suggestive of a previous unilateral ON [90].

In addition to subacute axonal loss following ON, patients experience ongoing loss of RNFL as a consequence both of MS itself and the normal aging process (as discussed above in Sect. 11.2). The majority of evidence to date suggests that the underlying rate of RNFL loss does not differ between MS eyes with and without previous ON [31, 33]; in other words, the significant insult to RNFL after ON is independent of, and does not affect, the insidious neurodegenerative processes ongoing in the majority of MS patients. In both of these studies, the effect of subacute axonal loss was removed from the analyses by excluding patients with a history of ON within the previous 6 months [31, 33].

In addition to pRNFL, the thickness of mRNFL is also reduced after ON in MS and CIS patients [18, 19, 28, 34] by, on average, just over 6 μm [28]. As in MS without confounding ON (Sect. 11.2), mRNFL may be of lesser utility as an outcome measure in MS and ON than pRNFL.

As with RNFL, GCIP thickness has almost universally been found to be reduced following an episode of ON in MS (Fig. 11.5) and CIS patients [18, 19, 28, 34, 36, 39, 72, 82, 83, 87, 91], with meta-analysis suggesting an average thickness loss of just over 16 μm [28]. Also similarly to RNFL, despite subacute loss of GCIP following ON, the underlying rate of GCIP loss does not differ between MS eyes with and without ON [31, 33]. Despite this similarity, GCIP offers important advantages over pRNFL as an outcome measure following ON. One factor already alluded to is that while approximately two thirds of ON patients present with retrobulbar inflammation of the optic nerve, the remaining third present with peripapillary oedema visible on fundoscopy [66]. (In fact, subsequent work employing OCT has suggested that as many as 82% of patients may have increased pRNFL thickness during the acute phase of ON [92], suggesting superior sensitivity of OCT at enabling detection of peripapillary oedema compared to traditional fundoscopy). A consequence of this is that pRNFL thickness during the acute phase of ON, when baseline OCT measurements are ideally acquired, is frequently increased relative to the fellow eye and/or control subjects due to inflammatory oedema [72, 82, 83, 91, 92]. Therefore, reduction of pRNFL thickness after the acute phase of ON cannot be ascribed to either resolution of oedema or axonal loss in isolation, and it has been suggested by some authors that it may be prudent to wait at least 3 months following an episode of ON before attempting to quantify pRNFL loss (Fig. 11.6) [8, 93]. In contrast, the evidence to date shows that GCIP thickness is not increased relative to that of unaffected contralateral eyes of ON patients [36, 91] or healthy control subjects [91, 94] during the acute phase of ON, and thus assessment of GCIP may enable earlier detection of inner retinal atrophy after ON in MS patients [83]. Supporting this hypothesis, thinning of GCIP appears to have plateaued by approximately 3 to 6 months following the clinical onset of ON [82, 83], a considerably shorter period than for pRNFL. Recent evidence suggests that analysis of inter-ocular differences in GCIP thickness is more sensitive in detecting a previous unilateral ON episode than pRNFL thickness differences [95]. An additional consideration is that GCIP may be less likely to be affected by the presence of non-pathological anatomical variations such as optic disc drusen or ectopically myelinated retinal nerve fibres. Despite these undoubted advantages of GCIP, pRNFL remains a useful and robust measure of retinal atrophy following ON, with the practical advantage that its segmentation and quantification is quicker and easier than that of GCIP. An understanding of the potential confounding factors described above will assist the clinician when assessing patients with ON using OCT.

With regard to the effects of ON upon the INL, results are more mixed than for the inner retinal layers, with some authors recording some small degree of INL thickening (Fig. 11.7) [18, 39, 91, 96] and others finding INL thickness comparable to normal values [34, 36, 72, 83]. Results may differ even between separate

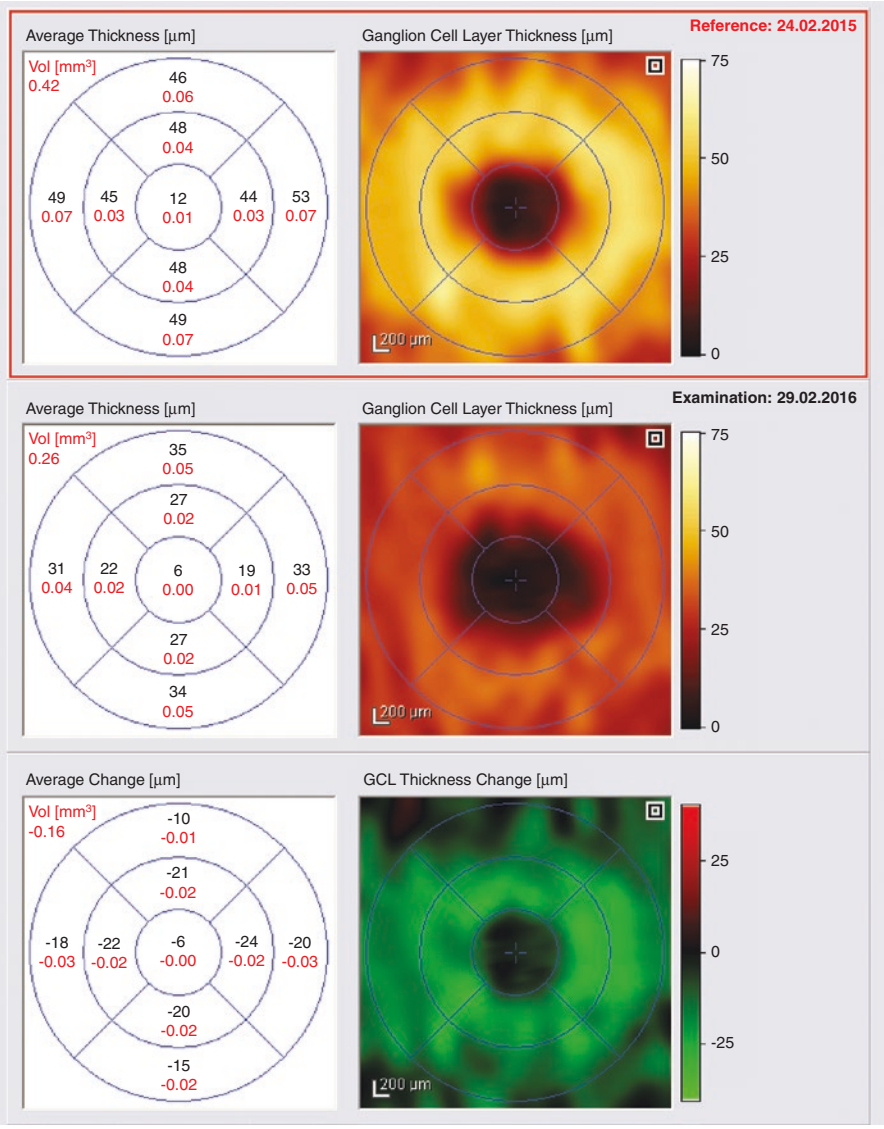

Fig. 11.5 OCT thickness maps of the ganglion cell layer (GCL) of a multiple sclerosis (MS) patient with optic neuritis (ON), showing OCT data acquired in the acute phase of ON (top) and 12 months later (middle). Atrophy of the GCL has followed ON, reflected in the thinner GCL at follow-up and in the negative thickness change values when the two examinations are compared (bottom). Although GCP is typically aggregated with the inner plexiform layer (IPL) as ganglion cell and inner plexiform layer (GCIP) for quantitative analysis, with this particular proprietary software it is not possible to generate thickness maps for GCIP and so only GCL is shown

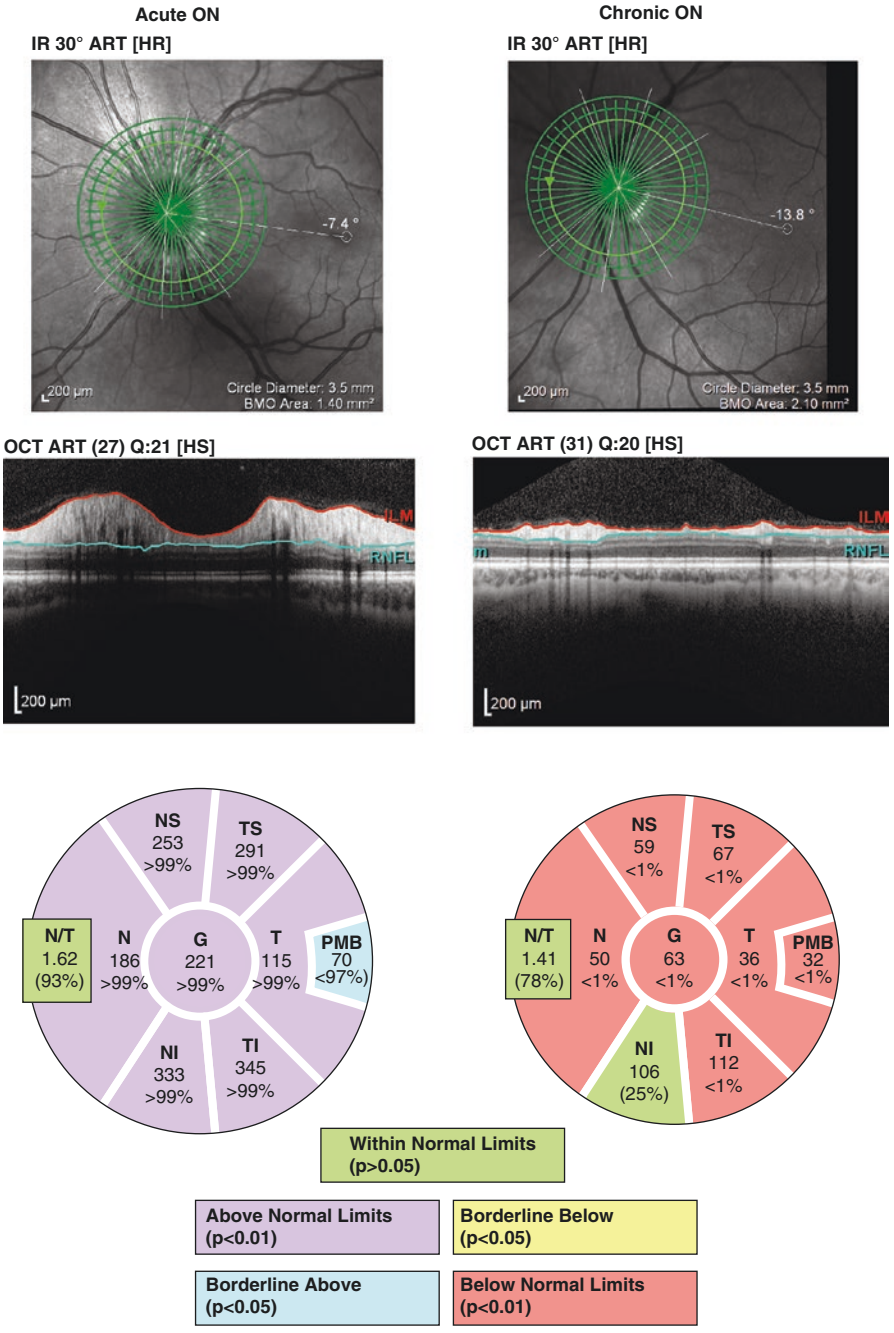

Fig. 11.6 OCT scans of the peripapillary retinal nerve fibre layer (pRNFL) in a patient with acute optic neuritis (ON) (left), and in a patient 12 months after ON (right). The patient with acute ON has inflammatory oedema around the optic nerve head, which is reflected in pRNFL thickness measurements significantly greater than normal values, whereas the patient with chronic ON shows significant atrophy of the pRNFL, with thickness values reduced compared to normal values

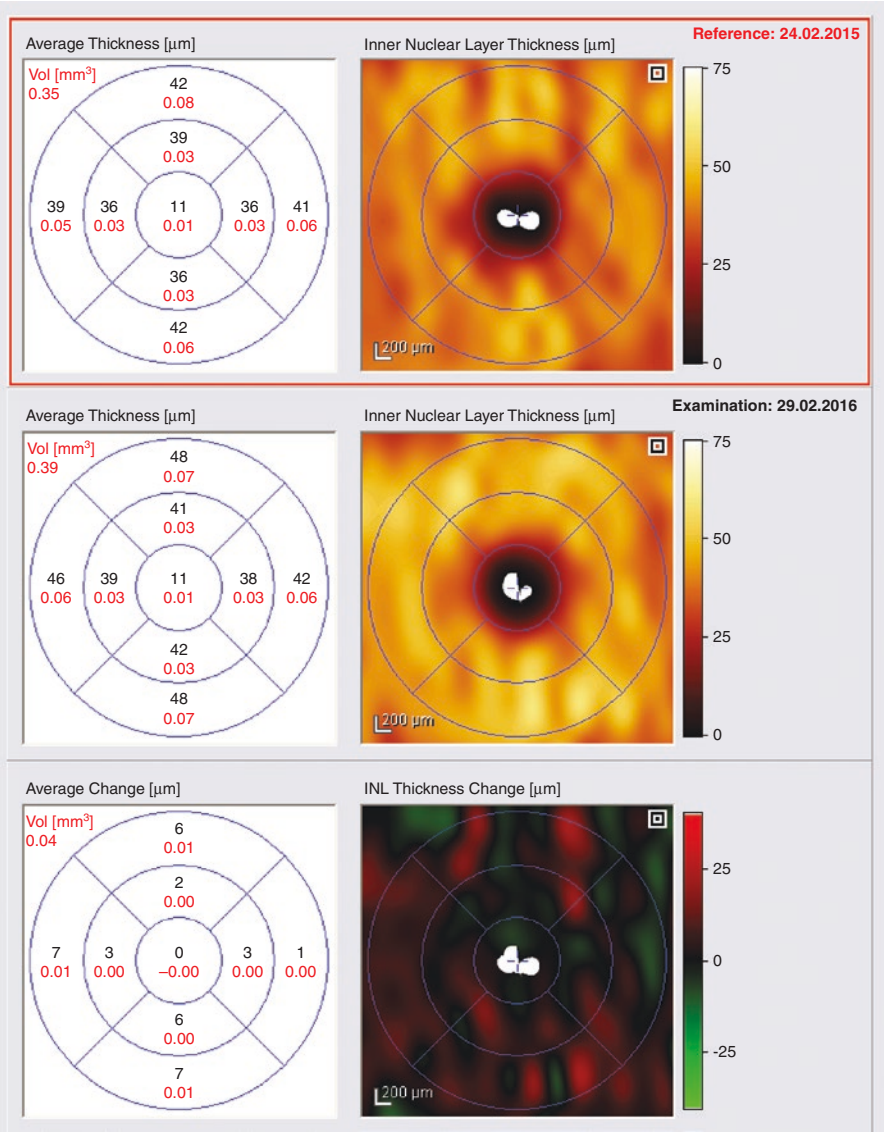

Fig. 11.7 OCT thickness maps of the inner nuclear layer (INL) of a multiple sclerosis (MS) patient with optic neuritis (ON), showing OCT data acquired in the acute phase of ON (top) and 12 months later (middle). INL is slightly thicker at follow-up, reflected in the small positive thickness change values when the two examinations are compared (bottom)

studies from the same laboratory [36, 91], which may reflect differences in sample size and thus statistical power. A meta-analysis including many hundreds of eyes detected an average macular INL thickening in MS eyes with previous ON of 0.77 µm relative to control subjects, and 0.61 µm relative to MS eyes without previous ON [28]. An important potential confounding factor associated with INL

assessment after ON is the link with microcystic macula oedema (MMO), discussed in detail in Sect. 11.5. Interpretation of previous work is made more difficult by the fact that some studies and versions of proprietary segmentation algorithms have aggregated INL and OPL [36, 91].

Similarly to the INL, previous studies have reported conflicting results regarding the influence of ON upon the OPL, with some reporting no influence of ON [36, 39, 72] and others reporting mild thickening [83, 91]. Aggregation of the OPL with the INL [36, 91] and ONL [72, 83] in the majority of studies may mask any possible ON-related effect restricted to the OPL; the only meta-analysis available to date, which also aggregated OPL and ONL, showed minimal thickening in the eyes of MS patients with previous ON relative to those of MS patients without previous ON, but not relative to those of healthy control subjects [28]. An additional confounding factor as revealed by longitudinal analyses is that the effect of ON upon the OPL and aggregated layers appears dynamic, varying as a function of time since [83, 91], and severity of [83], ON.

As with the INL and OPL, interpretation of the effects of ON upon the ONL is rendered challenging by the fact that the majority of studies have aggregated the ONL with other retinal layers such as the OPL [28, 72, 83] or photoreceptor segments [36, 91]. Again, the likely dynamic nature of any thickness changes represents an additional confounding factor [83, 91]. The only study to date which analysed ONL thickness in isolation found no measurable effect related to ON [39]. Thickness of PRL also seems to be unaffected by ON [39], although the current paucity of corroborative data is problematic when attempting to draw definitive conclusions.

Optic nerve perfusion, as measured by vessel density over the ONH using OCT-A, is reduced following ON in MS patients [61]. Current data regarding macular vessel density after ON is not unanimous, with an early study finding no differences between MS eyes both with and without ON and healthy control subjects [63], but more recent work recording that vessel density is reduced after ON [62, 64]. The reliability of OCT-A examination in MS patients with acute ON may be limited by technical issues such as reduced signal strength and shadowing phenomena exacerbated by inflammatory oedema at the optic nerve head.

11.4 Association of OCT Outcomes with Clinical, Structural, and Functional Measures in MS

Despite the manifold benefits of OCT, it remains fundamentally an examination of retinal and optic nerve head structure only; it is currently not possible to perform concurrent measurements of retinal, optic nerve head, or visual function in a manner analogous to (e.g.) functional magnetic resonance imaging (MRI) of the brain. In MS clinics and research settings, OCT is frequently combined with quantification of global disability and other structural (e.g., MRI) and/or functional (e.g., visual acuity, retinal and/or cortical electrophysiology) measures. Here, we examine the relationships between OCT and these different outcome measures.

11.4.1 Disability

Global disability in MS can be assessed using clinical scales such as the EDSS or the Multiple Sclerosis Functional Composite (MSFC). EDSS scores have been reported as being negatively correlated with RNFL [97–104], although this effect has not consistently been shown in all studies [105, 106]. EDSS also negatively correlates with GCIP thickness [97, 101, 102, 107], although not with TMV [100]. Significant correlations have also been recorded between EDSS and macular thickness in RRMS and SPMS, although not PPMS, patients [97]. Multiple Sclerosis Severity Score (MSSS) appears to be unrelated to RNFL thickness [106]. As the majority of MS disability scales may not sufficiently capture all aspects of disability beyond that in the realms of motor function and mobility, and in particular may not adequately reflect visual disability [108], the heterogeneous nature of results regarding the relationships between such scales and OCT is perhaps unsurprising. Despite this, OCT-derived TMV has been found to correlate with ambulatory ability in MS patients [109]. Rating scales focussed on visual function, such as the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) have been used successfully to capture subjective visual dysfunction in MS patients following ON [72, 110], and this approach may hold promise for future studies in the broader MS population.

In addition to cross-sectional associations with disability, OCT has also been shown to predict disability progression in MS patients. Patients with averaged pRNFL thickness of less than 87–88 μm at baseline were approximately twice as likely to show evidence of disability progression (measured by EDSS) over up to 3 years, and almost four times as likely over 5 years, as those with an RNFL thickness above this threshold at baseline [111]. The same study did not observe any prognostic power of TMV [111]. Another study also found that an averaged RNFL thickness of 88 μm was associated with a threefold increased risk of disability (EDSS) worsening over 3 years and a slightly lower, though comparable, risk of accumulating cognitive deficits over the same period [112]; a cross-sectional investigation has also shown a link between RNFL, as well as GCIP, with cognitive ability in MS patients [113]. Baseline atrophy of the temporal RNFL quadrant is associated with worsening of EDSS and increased risk of clinical relapses over 2 years [23], whilst averaged RNFL thickness has been shown to be of some utility in predicting a conversion to clinically definite MS over 12 months in CIS patients [114]. CIS patients with GCIP thinning are more likely to convert to MS within 3 years, and less likely to remain free of clinical disease activity, than those with thicker GCIP [115]. Finally, increased INL thickness at baseline is associated with a future increase in EDSS [116]. From these studies, it can be seen that OCT may enable clinicians to identify those MS and CIS patients at highest risk of relapses and disease progression, who may benefit from earlier and/or more efficacious treatment.

11.4.2 Magnetic Resonance Imaging (MRI)

MRI remains of vital importance in diagnosis and monitoring of MS patients, with improvements to conventional technology and the development of new imaging

techniques increasing sensitivity and permitting measurement of more diffuse CNS pathology [117]. To date, evidence suggests that RNFL thickness in MS patients is related to measures of brain parenchymal fraction (BPF) [118–120] and bicaudate ratio [101], with thinner RNFL being associated with greater brain atrophy, and also positively correlated with volume of both white and grey matter [23, 121]. However, the correlation between RNFL and grey matter may only be significant in more advanced MS, rather than at early stages of the disease [122], and some authors have reported that the relationship with white and grey matter may be significant only in eyes without previous ON [107, 121, 123]. RNFL thickness is also associated with MRI lesions in the optic radiations [17, 124, 125] and visual cortex [124]. However, RNFL appears not to be associated with non-specific MRI measures of MS disease activity such as T1 hypo-intense or T2 hyper-intense lesion volumes [23, 122]. GCIP is correlated with brain volume and white matter volume [121], but (as with RNFL) some of these relationships may be significant only in those eyes without previous ON [107, 123]. Faster rates of GCIP loss are associated with correspondingly increased rates of cerebral volume fraction (CVF; a measure of brain volume analogous to BPF) reduction, as well as cortical grey matter and thalamic atrophy, over a 4-year period [126]. INL thickening is associated with prospective T2 hyper-intense and gadolinium-enhancing lesion volume [116].

A particularly interesting aspect of the relationships between OCT and MRI parameters is the finding that different OCT-derived retinal structural measures may be correlated with different MRI outcome measures. For example, in MS eyes RNFL and GCIP thickness were positively correlated with both grey matter and caudate volumes, whilst INL thickness was correlated positively with fluid-attenuated inversion recovery (FLAIR) lesion volume and negatively with normal-appearing white matter (NAWM) volume [107]. The authors reported that whilst these correlations were true of their MS cohort as a whole, they were driven primarily by MS eyes without previous ON [107]. It has been proposed that these differences in the pattern of results between the inner (RNFL; GCIP) and outer (INL) retina may reflect pathologically distinct disease processes in MS [107], a hypothesis supported by subsequent work investigating the relationships between OCT and immune cells and immunoglobulin indices in cerebrospinal fluid (CSF) [116]. This subsequent study found that both GCIP and INL thickness were inversely correlated with CSF $CD19^{+}$ B-cell count, immunoglobulin G (IgG) and immunoglobulin A (IgA) synthesis, but that INL thickness was additionally positively correlated with $CD56^{bright}$ natural killer cell count [116].

Whilst all of these results are of interest, it remains challenging to compare the correlation of OCT findings with MRI parameters in MS patients due to the considerable heterogeneity in devices used, acquisition techniques, and analyses and outcome measures employed, particularly in MRI. Additional challenges arise from the fact that it is not currently possible to correlate MRI data from the brain as a whole with OCT data from individual eyes [127], and previous ON appears to affect correlations with MRI parameters in individual eyes considerably [121]. Whether OCT can to some extent replace MRI, along with the relative utilities of each technique, has been the subject of some debate [128, 129]. We suggest that whilst neither OCT

nor MRI are without disadvantages as tools for MS research, both will remain vital, complementary investigatory techniques in the future. Robust, long-term longitudinal data may enable better characterisation of the relative merits of both examinations [130].

11.4.3 Visual Function

Clinical tests of visual function have also been employed in the study of patients with MS. Perhaps the most fundamental and widely-used test of visual function is the measurement of visual acuity, in which the patient must correctly identify letters, numbers or symbols of diminishing size at a pre-defined test distance. In routine ophthalmological or optometric practice, the test is typically performed using black letters on a retro-illuminated white background, with contrast between target and background maximized; this measure is therefore described as high-contrast visual acuity (HCVA). By using grey letters instead of black, the contrast between letter and background is reduced (e.g., to 2.5% or 1.25% contrast rather than close to 100% in HCVA) and thus the measure becomes that of low-contrast visual acuity (LCVA). Examples of charts for measuring HCVA and LCVA can be seen in Fig. 11.8.

Patients with MS are frequently found to have reduced LCVA even when HCVA is normal [98, 131, 132], and thus LCVA is considered the more sensitive visual outcome measure in MS [132]. Reduced LCVA is correlated with RNFL thinning cross-sectionally [19, 22, 35, 97, 133–135] and longitudinally [133], although more strongly correlated with thinning of GCIP [19, 97]. LCVA correlates also with PMB thickness, TMV, and foveal volume [135]. Studies have also documented correlations between HCVA and RNFL [19, 22, 97, 133, 135], GCIP [19, 97, 133], and PMB [135] thickness, as well as TMV and foveal volume [135], although some of these relationships are likely to be weaker in comparison to 2.5% contrast LCVA [133] and have not been observed in all studies [35]. A clinically significant decrease in HCVA, 2.5% and 1.25% contrast LCVA is associated with a decrease in pRNFL thickness of 2.2, 3.3 and 3.3 μm as well as a decrease in GCIP thickness of 1.3, 1.9 and 2.4 μm, respectively [19].

In addition to impaired LCVA, patients with MS are commonly found to have impaired colour vision, in eyes both with and without a history of ON [70, 136], with up to two thirds of patients failing at least one screening test [136]. Studies using OCT have observed that performance in colour vision testing is strongly correlated with thickness of pRNFL [135, 137] and PMB [135, 137], as well as TMV [137], in MS patients. Given that the thicknesses of these retinal layers are reduced in MS eyes with previous ON relative to those without a history of ON [28, 29], it is intuitive that performance in colour vision testing appears worse in those eyes with previous ON [70, 135]. The correlations between OCT and colour vision outcome measures are stronger when using SD-OCT technology than with TD-OCT, likely reflecting the superior resolution and accuracy of the former [135].

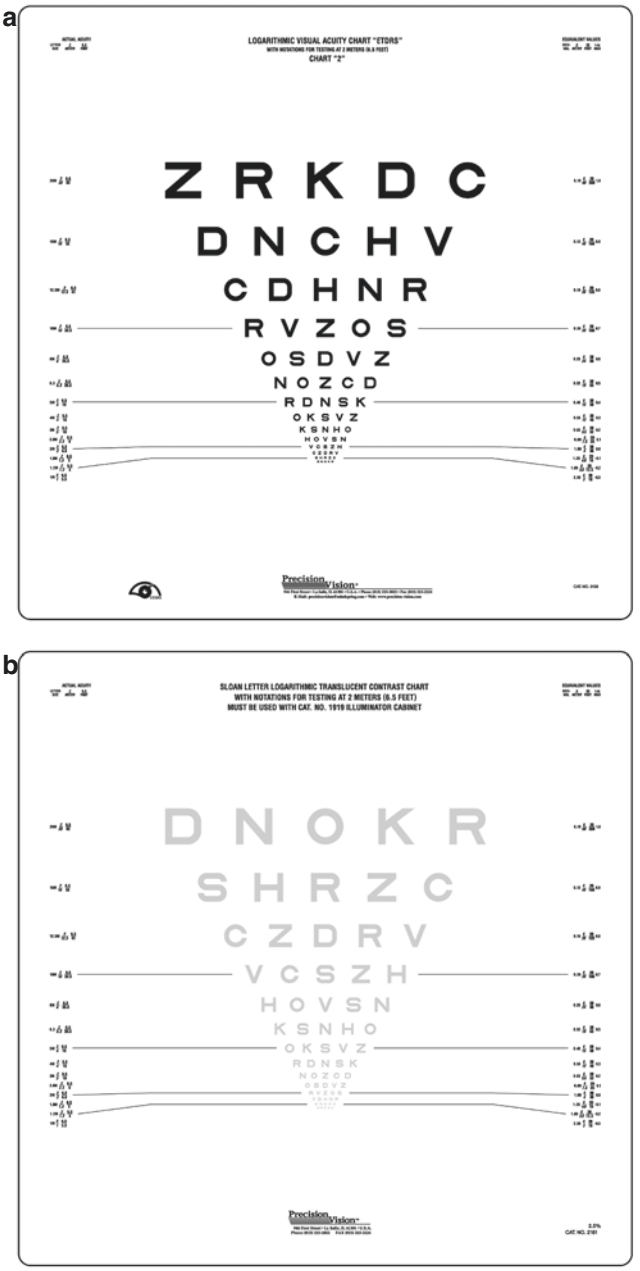

Fig. 11.8 Testing charts for measuring high- and low-contrast visual acuity (HCVA, LCVA). In order to measure HCVA, the contrast between target and background must be as close to 100% as possible, accomplished by using black targets on a white retro-illuminated background (**a**). Decreasing contrast can be accomplished by altering the colour of the targets from black to grey; the example chart shown here measures 2.5% contrast LCVA (**b**), but other contrast levels (e.g., 10%) are also possible. Images courtesy of Precision Vision, La Salle IL, U.S.A.

Perimetry, the subjective measurement of the visual field, may also be employed in order to ascertain the effects of disease on visual function. The technique is frequently utilized in patients with optic neuropathy (e.g. glaucoma), assessing the integrity of the entire visual pathway rather than specifically RGC or optic nerve function [138]. Visual field sensitivity (as measured by the mean deviation (MD) from age-matched normal values in decibels) is reduced in MS patients relative to normal subjects, with the greatest reduction being observed in those eyes with a history of ON [37, 139]. MD is correlated with TD-OCT-derived pRNFL thickness in MS eyes with a history of ON [140, 141]; at the time of writing, the quantitative relationship with deeper retinal layers remains unstudied. Given the high prevalence of fatigue symptoms in patients with MS [142] and the adverse effects of fatigue on both visual sensitivity and reliability when performing perimetry [138], it is likely that more objective measures of visual function, less dependent on alertness and cognitive performance, may be of more utility when studying patients with MS.

11.4.4 Electrophysiological Assessment of the Visual Pathway

Electrophysiological tests such as the visual evoked potential (VEP) and electroretinogram (ERG) quantify the electrical response of the visual cortex and retina, respectively, in response to precisely-defined visual stimuli. Using the ERG, the function of the photoreceptors and bipolar cells over the entire retina can be measured [143]. The multifocal ERG (MF-ERG) also measures the function of the photoreceptors and bipolar cells [144], but from discrete regions of the macula only [145]. The function of the ganglion cells of the inner retina can be measured using the pattern electroretinogram (PERG) or the photopic negative response (PhNR) of the ERG [146, 147]. The multifocal VEP (MF-VEP), in a manner analogous to the MF-ERG, allows functional assessment of smaller, localized areas of cortex and smaller bundles of axons in the visual pathway [148]. The utility of MF-VEP in clinical routine remains debated by experts in the field for a number of technical reasons, however it remains frequently used within MS research [35, 114, 149–152].

A number of studies have recorded significant correlations between electrophysiological and OCT parameters in MS patients. The response latency of the VEP or MF-VEP is correlated with mean RNFL thickness [35, 99, 153, 154], TMV [153], and GCIP thickness [35]. Evidence suggests that this relationship with RNFL is significant in eyes both with and without a history of ON but stronger in ON eyes [99]. Combining OCT measures of RNFL thickness with VEP ensures greater sensitivity in detecting anterior visual pathway damage after ON in MS patients than using either test alone [99]. PERG amplitudes are correlated with pRNFL thickness [37, 153, 154], TMV [153], GCIP thickness [37], and total retinal thickness [37]. Normalized PERG amplitudes (the ratio of the amplitudes of the N95 and P50 components) are also correlated with TMV [153, 154]. PhNR is correlated with RNFL thickness in MS eyes without previous ON and with an ON event at least 6 months previously, but not those with a history of ON less than 6 months previously [155];

this finding likely reflects the temporal dynamics of RNFL loss after ON as discussed in Sect. 11.3. The cone-driven ERG b-wave response latency has also been found to inversely correlate with RNFL and GCIP thickness, although its predictive power for these OCT parameters was significantly weaker than was the MF-VEP latency [35], doubtless reflecting the fact that this ERG component is generated by the bipolar cells and not the ganglion cells or their axons [156]. More recent work has documented some degree of negative correlation between ERG a-wave amplitudes and ONL thickness, as well as ERG b-wave amplitudes and INL thickness, in MS patients [39]; however, this study (and others) also recorded that ERG amplitudes are mostly normal in MS patients [35, 39, 46, 157–159]. Conversely, the latency of the ERG, particularly those responses driven in whole or in part by the cone system, has been shown to be abnormal to varying degrees in MS patients [35, 39, 46, 47, 157] whilst being uncorrelated with OCT-derived measures of ONL or INL [39]. This lack of correlation is compatible with dysfunctional, but not atrophic, photoreceptors and bipolar cells in patients with MS. The same study also failed to observe any correlations between MF-ERG parameters and INL structure, despite recording evidence of abnormal MF-ERG P1 latency [39].

With modification of the standard MF-ERG test protocol it is possible to visualize an additional component of the MF-ERG, the optic nerve head component (ONHC), which is generated at the optic nerve head [160]. Abnormalities of the OHNC have been documented in the ipsilateral and (to a lesser extent) contralateral eyes of MS patients with a history of unilateral ON [161]. The number of abnormal ONHC responses correlates strongly with RNFL thickness, so that a 10 μm reduction in pRNFL thickness is associated with 6.8 additional abnormal ONHC responses (from a total of 103 responses) [161]. The relationship between the ONHC and other OCT parameters remains unclear at the time of writing.

11.5 The Inner Nuclear Layer (INL)

Recent years have seen the emergence of interest regarding the potential importance of OCT-derived measurements of the INL in patients with MS. The INL contains the nuclei of the second-order retinal neurons, bipolar cells, as well as horizontal cells, amacrine cells, and the cell bodies of Müller glia [162]. This recent interest was arguably initially driven by an influential post-mortem histological study which recorded atrophy of the INL in addition to the ganglion cells [48]. Other authors, using OCT, have suggested that INL (in addition to ONL) may be reduced in thickness in a subset of MS patients exhibiting a severe clinical phenotype [42], and that increased INL thickness is associated with higher levels of disease activity, as evidenced both clinically and through MRI [163]. In addition, it has been proposed that the INL responds dynamically to MS disease activity and treatment; untreated MS patients were found to have a greater INL volume than healthy control subjects, yet this volume appeared to normalise following successful disease-modifying therapy (as evidenced by no clinical relapses or new MRI lesions during the follow-up period) yet remain elevated in patients in whom therapy was unsuccessful (Fig. 11.9) [24]. A particularly noteworthy aspect of this work [24] is that eyes with previous ON were excluded

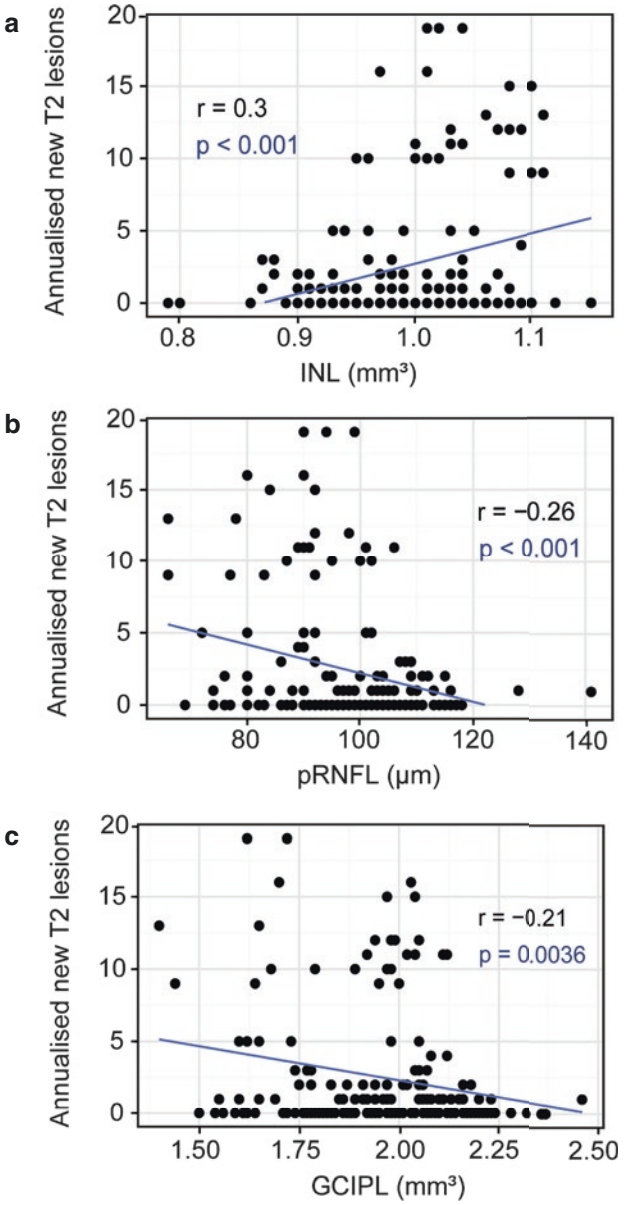

Fig. 11.9 Correlations between baseline inner nuclear layer (INL) volume (**a**), peripapillary retinal nerve fibre layer (pRNFL) thickness (**b**), and ganglion cell and inner plexiform layer (GCIP) volume (here named GCIPL; **c**) and prospective multiple sclerosis (MS) disease activity, as measured by annualised development of new T2 lesions visible using magnetic resonance imaging (MRI). INL volume is positively correlated with the number of new lesions, meaning that higher baseline INL volume is associated with an increased chance of developing new T2 lesions. Conversely, pRNFL thickness and GCIP volume are negatively correlated with the development of new T2 lesions, meaning that higher pRNFL thickness/GCIP volume is associated with a decreased chance of developing new lesions. Adapted from Knier et al. Brain 139, 2855–2863 (2016) with the permission of Oxford University Press and Prof. Thomas Korn

from analysis, ensuring that measures of INL thickness were uncontaminated by potential post-ON thickening [28]. Given that INL does not show atrophy after ON despite the well-documented thinning of the adjacent inner retina [18, 28], it may be that changes to INL thickness reflect inflammatory, rather than neurodegenerative, processes in MS [24].

Microcystic macular oedema (MMO) may also be observed in the INL of patients with MS. MMO was initially described as discrete, cyst-like spaces, visible on at least two adjacent OCT B-scans and predominantly confined to the INL, in 4.7% of MS patients (Fig. 11.10); these patients had, on average, higher EDSS and MSSS scores and reduced visual acuity, and were more likely to have previously suffered an episode of ON, in comparison to those without comparable changes to the INL [164]. These findings appear to be transient in the majority of patients (Fig. 11.11) [165]. The appropriate nomenclature of these findings has been a subject of debate; whilst originally described as microcystic macular oedema [164], the intraretinal

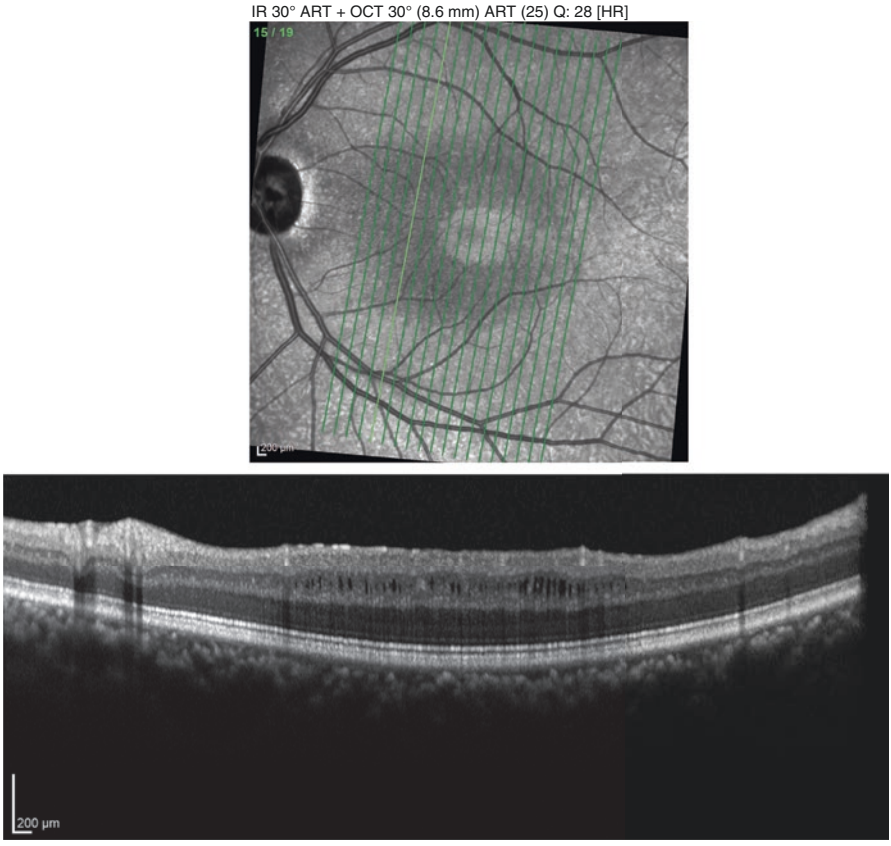

Fig. 11.10 OCT B-scan of the left eye of a patient with multiple sclerosis (MS) and microcystic macular oedema (MMO). The B-scan shows cystoid lesions confined to the inner nuclear layer (INL), pathognomonic for MMO

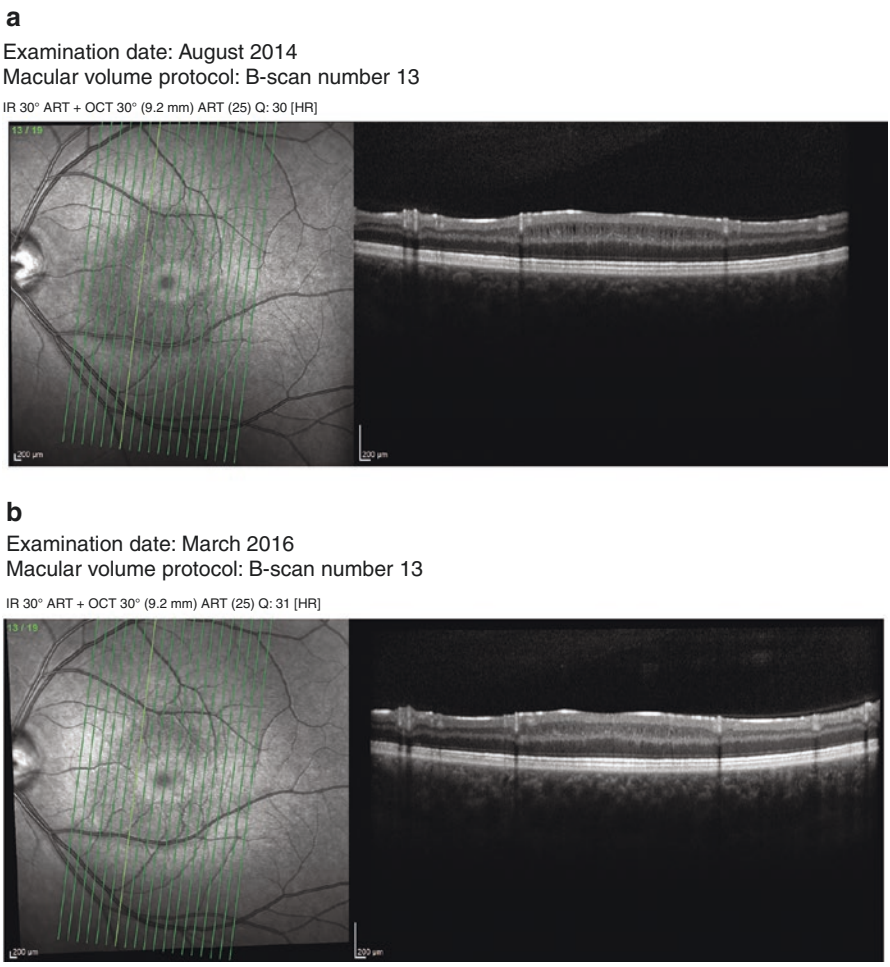

Fig. 11.11 Illustration of the transient nature of microcystic macular oedema (MMO) in a multiple sclerosis (MS) patient. The initial OCT scan revealed the presence of microcystoid lesions in the inner nuclear layer (INL), thereby confirming MMO in this patient (**a**). At follow-up 19 months later (at the same retinal location, as seen by the identical B-scan numbers), no more cystoid lesions were visible, indicating resolution of MMO (**b**)

spaces appear not to be lined with epithelium and are therefore not truly cystic, but rather cystoid, in nature [166]. When associated with optic atrophy, it has been suggested that INL thickening with or without cystoid lesions in the INL should be termed 'retrograde maculopathy' [167]. Nevertheless, the term MMO has persisted and will be used for familiarity here.

Although MMO was initially described in MS patients [163, 164], particularly in those with a history of ON [163, 164, 168], it rapidly became apparent from subsequent reports that MMO-like OCT findings can be observed in a range of non-MS disease states, including neuromyelitis optica spectrum disease (NMOSD)

[168–170], relapsing isolated optic neuritis (RION) [171], chronic relapsing inflammatory optic neuropathy (CRION) [168], glaucoma [172, 173], Leber's hereditary optic neuropathy (LHON) [174], dominant optic atrophy [174, 175], chronic compressive optic neuropathy secondary to glioma in a patient with neurofibromatosis type 1 [176], Tanzanian endemic optic neuropathy [177], traumatic optic neuropathy [172], hydrocephalus [172], tobacco-alcohol optic neuropathy [178], following phacoemulsification [179], and consequent to combined vitrectomy and inner limiting membrane removal [180]. The finding that cystoid changes in INL are observed post-vitrectomy (i.e., following surgical removal of the vitreous body) [180] is particularly relevant, as it provides clear evidence against previous hypotheses [174, 175] that vitreo-retinal traction is necessary for the formation of MMO, but is consistent with the proposal that MMO can occur independently of vitreo-retinal traction [170]. Changes in INL volume such as that seen in MMO have been hypothesised to be mediated by the Müller glial cells (the cell bodies of which are found in the INL) [171], and as potentially representing evidence of a glymphatic system (similar to that found in the brain) within the retina [181].

Despite a considerable lack of specificity, it is important to recognize that MMO in MS patients has to date, without exception, been found to be associated with increased disease severity [163, 164, 168]. This increased severity is observed in OCT scans as decreased RNFL [164] and GCIP [163] thickness, as well as increased INL thickness [163]; currently, there is no unanimity with regard to differences in TMV between MS eyes with and without MMO [164, 168]. Clinical indicators of increased disease severity in MS patients with MMO are reduced HCVA [163, 164, 168] and LCVA [163], higher MSSS values [163, 164, 168], higher EDSS values [164, 168], as well as an increased likelihood of developing Gadolinium-enhancing and T2-weighted MRI lesions [163]. African-American MS patients have a higher prevalence of MMO [51], consistent with the more aggressive disease course typically observed in this population [49–52]. Thus, a finding of MMO upon OCT examination may assist clinicians in their decision-making process when considering, for example, whether to recommend medical treatment (or a more efficacious treatment) to a MS patient. It may also lead the clinician to consider the possibility of an earlier insult to the optic nerve and initiate further diagnostic tests, for example VEP.

Although the evidence to date suggests that the INL is of great importance in MS, and may reflect inflammatory processes and response to treatment, at the time of writing the body of research is still nascent and thus the precise role of the INL arguably remains unclear. OCT-derived measures of INL structure may be confounded both by ON [28] and MMO, as discussed above, in patients with MS. An additional potential confound is that the INL contains nuclei of bipolar cells in addition to horizontal cells, amacrine cells, and the cell bodies of the Müller glia [162], meaning that structural changes to INL may be of multiple aetiologies and may not be ascribed to specific cell types (neuronal or glial) or specific types of neuron. Functional tests such as the ERG may measure bipolar integrity in isolation, however abnormal functional parameters appear not to correlate with OCT-derived INL structural measures [39]. More detailed characterisation of the role of the INL in MS, including longitudinal studies, is necessary.

11.6 OCT Findings in Experimental Models of MS

Although OCT has become a prominent tool in the clinical setting of MS diagnosis, it has only more recently begun to be explored in experimental animal, particularly rodent, models. Human and murine retinae share a similar laminar structure, with the primary difference between the two species being the lack of fovea in mice [182]. Therefore, the majority of studies utilizing OCT in murine models have obtained scans centred upon the optic nerve head, which provides a clear anatomical landmark for consistent longitudinal measurements (Fig. 11.12). OCT measures in mice are robust, with studies finding almost constant inner retinal layer (IRL)

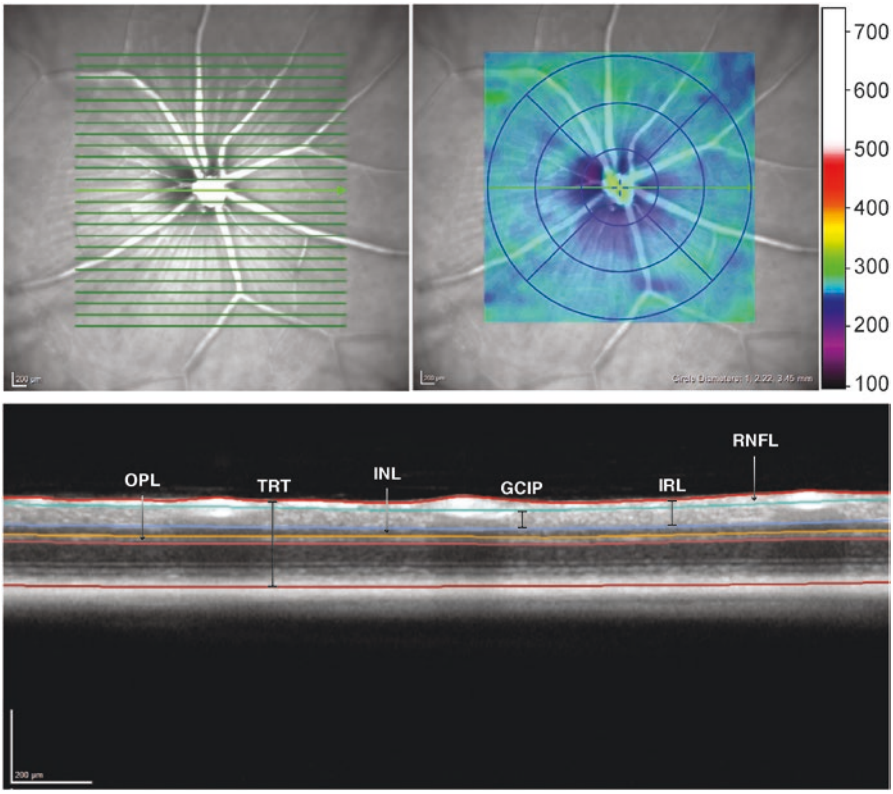

Fig. 11.12 Illustration of a typical scan in a healthy C57BL/6J (wild-type) mouse. The volume scan is centred upon the optic nerve head, rather than the fovea. After manual segmentation, the retinal layers can be defined as seen in the bottom panel: the retinal nerve fibre layer (RNFL) and ganglion cell and inner plexiform layer (GCIP) are aggregated together to give a thickness measure of the inner retinal layers (IRL), whilst the inner nuclear layer (INL) and outer plexiform layer (OPL) are analysed separately. A coarse but reliable measure of retinal structure is provided by the total retinal thickness (TRT), reflecting the thickness of all retinal layers combined

thickness over time in healthy controls [183–185] and excellent test-retest reliability [185, 186].

An early study utilizing a custom-built OCT device assessed the visual pathway in a transgenic mouse model of MS (using ND4 mice), in which animals spontaneously undergo demyelination after 3 months of age [187]. Qualitative OCT assessments of the retina and the optic nerve head areas were not significantly different between control mice or ND4 mice even though impaired ganglion cell function (as evidenced by reduced PERG amplitudes) was observed [187]. Furthermore, the authors observed no difference between groups when evaluating immunohistochemical retinal ganglion cell markers [187], suggesting that the ND4 murine model of MS may not be the most suitable for assessing structural damage to the visual pathway.

Experimental autoimmune encephalomyelitis (EAE) is an older and more widely employed model of MS, in which animals are injected with CNS proteins such as myelin oligodendrocyte glycoprotein (MOG) emulsified in an adjuvant, inducing an inflammatory response. Immunised animals develop demyelinating lesions in the CNS, including the optic nerve and retina [188–190]. Between 70–92% of eyes in these animals develop ON, making the model ideal for investigating therapies targeting visual impairment [78, 183, 185].

GCIP thinning around the optic nerve head has been observed in EAE mice 23–25 days post immunisation (dpi) compared to healthy control animals [191]. Similarly, significant RNFL thinning has been observed in EAE, specifically in the later stages of the disease course [186, 191, 192]. A previous study using EAE rats also recorded significant RNFL thinning prior to clinical manifestation of the disease [186], however another report in EAE mice did not observe differences in RNFL thickness relative to controls at similarly early timepoints [192]. These differences may be due to the use of different animal species (mouse vs. rat) and immunisation ($MOG_{35–55}$ vs. $MOG_{1–125}$). An additional consideration is that the RNFL is a relatively thin layer in rodents compared to humans and it is difficult to distinguish between the RNFL and the ganglion cell layer, and therefore difficult to accurately and reproducibly quantify.

More recent studies have addressed this issue by aggregating the RNFL, GCL and IPL together; this complex is known as the IRL and provides a more robust measure of EAE-induced neuro-axonal degeneration [183–185]. IRL thickness significantly increases at clinical onset of the disease in EAE mice, followed by a steady decline as the disease progresses [185]. Another study following EAE mice up to 4 months post-immunisation found a continued and steady decline in IRL thickness throughout the later stages of the disease [183]. These findings resemble the initial RNFL thickening followed by neuroaxonal degeneration observed in many human studies of ON in MS, as summarised in Sect. 11.3. Interestingly, similar findings were also observed in a model of chronic MS, where IRL thickening was perceived after 2 weeks of EAE followed by significant thinning after 8 weeks of disease compared to healthy controls [184]. There is also evidence for early neurodegeneration in the retina, which may be initially masked by inflammatory oedema and become more visible only at later

timepoints, after the inflammation has reduced [184–186]. Total retinal thickness (TRT) also increased during peak disease and decreased during recovery of clinical symptoms in EAE mice [191]. Since the TRT by definition includes the IRL, the increase in thickness at earlier time points is consistent. Conversely, INL thickness did not change during the disease course in both healthy and EAE mice [191]. However, this is a relatively thin structure and with currently available segmentation tools, involving primarily manual correction, it is challenging to obtain reliable measures of INL in mice.

As in humans [193], OCT findings of rodent retinal thickness correlate significantly with histological measurements of the retina at various time points in the disease course [184, 186, 194]. Discrepancies between retinal histology and OCT measurements can be attributable to tissue shrinkage following fixation [186]. Therefore, *in vivo* OCT measurements of the retina may provide a more accurate representation of retinal thickness changes compared to post-mortem histological analysis. OCT measures of IRL thinning are also inversely correlated with functional measures of visual impairment such as spatial frequency optokinetic response thresholds [183]. MRI measures of the visual pathway correlate strongly with OCT findings in EAE. Earlier in the disease course, IRL thickening correlates with T2 signal hyperintensities in the optic nerve, providing further support for inflammation in EAE mice [185]. Conversely, IRL thinning in later stages of the disease is associated with changes in the optic nerve [184, 185] and optic tracts [185] as detected with DTI, consistent with retrograde degeneration in the retina originating from lesions in more posterior parts of the visual pathway. However, the literature to date is not unanimous regarding the relationship between EAE scores and OCT measures, as one study recorded a significant negative correlation between EAE scores and IRL thickness [183], and others have reported no relationship [184, 185]. The EAE score does not incorporate visual outcomes but rather focuses on measurements of motor impairment, and therefore the lack of correlation observed in some studies may be due to atypical mice that present with ON and retinal damage but exhibit little or no clinical disability.

Overall, the retinal thinning observed longitudinally in EAE mice is representative of neuro-axonal degeneration independent of demyelination. This retinal degeneration in EAE parallels that observed in ON in humans (Sect. 11.3) but occurs in a much shorter time frame, making OCT an ideal tool for use in pre-clinical trials. The fact that structural damage to the visual pathway can precede clinical symptoms in EAE reinforces the need for early therapeutic interventions in ON.

Increasingly, pre-clinical trials in experimental models of MS are using OCT to assess structural damage to the anterior visual pathway and neuro-axonal degeneration following ON. For example, one such trial studied EAE-$MOG_{35–55}$ mice which had been injected with antibodies against IL-17, a pro-inflammatory cytokine which is thought to play an important role in the development of ON and axonal atrophy in EAE. RNFL and GCIP were both significantly thicker in mice treated with anti-IL-17 compared to untreated EAE mice, and discontinuing anti-IL-17 treatment after the peak of clinical symptoms did not increase RNFL thinning [191]. This

suggests that damage to the optic nerve and retina in EAE may occur, at least partly, due to an IL-17 mediated inflammatory response.

Another pre-clinical trial examined the effect of gypenosides, which are saponins with antioxidative and neuroprotective properties extracted from the *Gynostemma pentaphyllum* plant [192]. The authors administered either daily injections of gypenoside monotherapy with three different densities, methylprednisolone, or a combination of the two treatments to $MOG_{35–55}$ immunized EAE mice. Attenuation of RNFL degeneration was observed in mice treated with gypenoside and combination therapy compared to untreated EAE mice 30 dpi [192]. Interestingly, at 40 dpi, RNFL thinning was observed in both untreated EAE mice and in mice treated with methylprednisolone compared to healthy controls, suggesting that gypenoside, rather than methylprednisolone, may have neuroprotective effects [192]. Results of previous human studies have suggested that corticosteroids may reduce the severity of symptoms at presentation but are not protective against neurodegeneration [75, 195], a finding reinforced by these more recent murine OCT findings [192]. Although gypenoside was not directly linked to decreased inflammation, it does appear to have some effect on reducing demyelination in the visual pathway, while a combination of both gypenoside and methylprednisolone appeared to have the best effect on reducing demyelination in the acute phase of ON [192].

Most recently, a pre-clinical OCT trial [183] was performed using alpha-lipoic acid (LA), a naturally occurring sulfhydryl compound with strong antioxidant and anti-inflammatory properties [196, 197]. In this study [183], LA was offered both as prophylactic and therapeutic treatment for mice immunised with EAE-$MOG_{35–55}$. Prophylactic LA treatment appeared to reduce IRL degeneration in EAE mice, while therapeutic treatment had no effect on IRL [183]. Therapeutic LA resulted in reduced clinical disability and preserved ganglion cells, yet IRL thinning and functional visual impairment was still observed [183], suggesting that early damage to IRL cannot be repaired or protected by LA administered after clinical disease onset. This suggests that early therapeutic intervention is essential to reducing degeneration following acute ON. Though these pre-clinical trials provide promising prophylactic treatment options in mice, there is still a need for viable therapeutic treatment options for ON in humans, as clinical trials usually involve treatment after the onset of clinical symptoms of ON, when the opportunity for prophylaxis has passed.

11.7 Summary

Patients with MS without previous ON exhibit thinning of the inner retina (pRNFL; GCIP), but not of the deeper layers such as INL, OPL, ONL, and PRL. Eyes with previous ON exhibit, on average, significantly more thinning of the inner retina. Although there is credible evidence of mild INL thickening in MS eyes with previous ON, this appears to be smaller in magnitude and more variable. Interpretation of OCT results pertaining to OPL, ONL, and PRL (and, to a lesser extent, the INL) is complicated by inconsistency of aggregation of these layers between different

studies and software versions, although it appears that any documented changes to the thickness of these layers occur only after ON, are dynamic in nature, and also of considerably lesser magnitude than those observed in the inner retinal layers. With these factors in mind, we suggest that future studies examining outer, rather than inner, retinal structure in MS patients with or without ON may require much larger cohorts in order to achieve sufficient statistical power to detect potentially small differences between patient groups. OCT can be used to identify those patients at risk of a rapid or severely disabling disease course, and initiate timely intervention. In particular, analysis of the INL may in future assist in differentiating degenerative from inflammatory disease activity, and in monitoring treatment efficacy. Although it is unlikely to replace MRI, OCT provides valuable complementary information in patients with MS. OCT-A holds promise as a new outcome measure in MS, although at the time of writing the body of research is still nascent. Findings from studies using experimental models of MS may inform the clinical development of future prophylactic and/or therapeutic neuroprotective treatments for use in humans.

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