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Recent advances and future directions on the use of optical coherence tomography in neuro-ophthalmology

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Abstract:

Optical coherence tomography (OCT) is a noninvasive imaging technique used to qualitatively and quantitatively analyze various layers of the retina. OCT of the retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer (GCIPL) is particularly useful in neuro-ophthalmology for the evaluation of patients with optic neuropathies and retrochiasmal visual pathway disorders. OCT allows for an objective quantification of edema and atrophy of the RNFL and GCIPL, which may be evident before obvious clinical signs and visual dysfunction develop. Enhanced depth imaging OCT allows for visualization of deep structures of the optic nerve and has emerged as the gold standard for the detection of optic disc drusen. In the evaluation of compressive optic neuropathies, OCT RNFL and GCIPL thicknesses have been established as the most important visual prognostic factor. There is increasing evidence that inclusion of OCT as part of the diagnostic criteria for multiple sclerosis (MS) increases its sensitivity. Moreover, OCT of the RNFL and GCIPL may be helpful in the early detection and monitoring the treatment of conditions such as MS and Alzheimer's disease. OCT is an important aspect of the neuro-ophthalmologic assessment and its use is likely to increase moving forward.

Keywords:

Diagnostic techniques, ophthalmological, ophthalmology, optical coherence, tomography

Introduction

Optical coherence tomography (OCT) is a noninvasive imaging technique that provides high resolution images of the retina and optic nerve.[1] While OCT was originally used in diagnosing diseases of the retina and then in glaucoma, this technology is increasingly being used to evaluate patients with afferent neuro-ophthalmic conditions and has become the standard of care for evaluating patients with various optic neuropathies.[2] The retina is composed of multiple layers of neural tissue which can be differentiated by varying levels of signal on OCT. Two important retinal layers in evaluating patients with optic neuropathies are the ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL). The former contains the cell bodies of the retinal ganglion cells, whereas the latter contains the axons which eventually synapse with the lateral geniculate nucleus. The inner plexiform layer and the GCL are often segmented together on OCT devices and collectively referred to as the ganglion cell–inner plexiform layer (GCIPL).

Recent advancements in OCT include new modalities such as swept-source (SS) OCT, enhanced depth imaging (EDI) OCT, *en face* OCT, and OCT angiography (OCT-A).[3-6] Initial OCT methods had poor visualization of the deeper layers of the retina beyond Bruch's membrane due to scattering of light at the retinal pigment epithelium (RPE). EDI-OCT allows for visualization of the deep portions of the choroid, which is implicated in many retinal diseases, and the deep structures of the optic nerve.[6] SS-OCT

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allows for penetrance to the level of the choroid at the expense of slightly reduced axial resolution.[7] *En face* OCT produces transverse images of the retinal layers allowing for evaluation of morphological changes in the coronal view similar to fundus photography.[5] OCT-A visualizes the retinal vasculature without the use of fluorescein dye with much greater resolution than traditional angiography.[8] Collectively, these advancements have expanded the utility of OCT, making it one of the most important ancillary tests in ophthalmology. In this study, we review the utility of OCT in the evaluation of various optic neuropathies and afferent visual pathway disorders seen in neuro-ophthalmology.

Optical Coherence Tomography in the Evaluation of Optic Neuropathies

Optic disc drusen

Optic disc drusen (ODD) are calcified deposits of axonal metabolic products within the prelaminar tissue of the optic nerve.[9] Many patients with ODD are asymptomatic, but ODD can cause transient visual obscurations, be mistaken for papilledema, or increase the risk for nonarteritic anterior ischemic optic neuropathy (NAION) due to crowding at the optic nerve head (ONH).[10-12] Historically, ODD were diagnosed using imaging modalities such as B-scan ultrasound, fundus autofluorescence (FAF), and computed tomography (CT).[13] EDI-OCT, however, has been shown to be superior compared to previous methods when evaluating ODD due to better resolution when imaging the deep ONH structures.[10,14-16] A primary limitation was that the majority of ODD are "buried" and difficult to visualize on examination and on B-scan ultrasound. For visible ODD, EDI-OCT and B-scan ultrasound have similar sensitivity, but there is recent evidence to suggest that EDI-OCT can identify buried ODD not seen on B-scan ultrasound.[14,17,18] EDI-OCT has offered improvements to the detection of noncalcified and buried drusen compared to B-scan ultrasound, FAF, and CT.[14,15,19,20] Therefore, EDI-OCT is particularly useful in younger populations where a greater proportion of ODD are buried.[11,15,20,21] An example of ODD seen with FAF and EDI-OCT is shown in Figure 1.

EDI-OCT has changed the way ODD are diagnosed, has further elucidated other peripapillary structures, such as peripapillary hyperreflective ovoid mass-like structures (PHOMS) and hyperreflective horizontal lines, and has provided a way to predict visual prognosis in patients with ODD. The Optic Disc Drusen Studies (ODDS) Consortium has made recommendations for consistent diagnostic criteria using OCT.[10] ODD are defined as hyporeflective structures that are located above the lamina cribrosa and have a hyperreflective margin.[10] Hyperreflective horizontal lines often seen on OCT of the optic nerve, with and without ODD, were previously thought to be nascent ODD. However, because there are still questions if the horizontal lines were from the lamina cribrosa, and or if they represent some other peripapillary finding, the ODDS Consortium does not include these findings in the definition of ODD.

PHOMS, hyperreflective structures seen on OCT, received increasing attention with the introduction of EDI-OCT as they were not previously seen on B-scan ultrasound or FAF due to lack of calcifications.[15] They were originally thought to be precursors to ODD. Histological analysis of PHOMS, however, demonstrated that they are more similar to the distended axons seen in papilledema.[22] Studies have suggested that PHOMS are caused by prelaminar axonal distension due to anomalies of the ONH and are not specific to ODD.[22] PHOMS have been seen in a number of other pathologies of the ONH including the numerous causes of optic disc edema.[23] Most recently, OCT-A showed that PHOMS contain a complex vascular structure, which represent a divergence from the pathogenesis of ODD.[24] This highlights the growing sentiment that PHOMS should be viewed as a separate phenomenon and not diagnosed as ODD.[10]

Visual prognosis in patients with ODD has been suspected to correlate with the volume of the ODD, but was difficult to predict prior to the availability of EDI due to challenges identifying buried ODD.[25] In several studies using EDI-OCT to evaluate ODD, it has been found that larger ODD are correlated with reduced RNFL thickness and worsening visual field loss.[26,27] Recent studies have suggested that the association with GCIPL thinning could be even greater and may result in a greater emphasis on the GCIPL as a

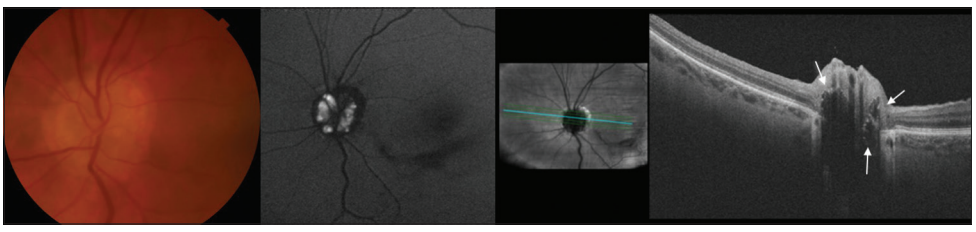

Figure 1: Optic disc drusen can be seen in color fundus photos and autofluorescence. Optical coherence tomography HD-5 line raster using the enhanced depth imaging protocol shows three regions of hyporeflectivity with hyperreflective margins corresponding to drusen seen in the photos

predictor of functional decline in ODD.[26] EDI-OCT has also showed that ODD are highly associated with the development of NAION in younger patients without vascular risk factors.[11,21] This is likely the result of ODD predisposing them to an axonal compartment syndrome.[11,21]

Optic neuritis, multiple sclerosis, and neuromyelitis optica spectrum disorders

Optic neuritis can be idiopathic or related to multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSD), aquaporin-4-immunoglobulin (Ig) G, and myelin oligodendrocyte glycoprotein (MOG)-IgG.[28] It has long been known that RNFL and GCIPL thinning occurs in optic neuritis and MS, and that these changes correlate with visual dysfunction.[29] OCT is able to quantify the thickness of different retinal layers impacted by optic neuritis and may be helpful in the acute and chronic period.[30,31]

Spontaneous recovery without treatment is typically expected in optic neuritis, but residual thinning of the RNFL occurs due to retrograde degeneration [Figure 2].[32] Monitoring absolute measures of RNFL or GCIPL layers are used, but this method can be problematic as some individuals may have variation in thickness at baseline.[33,34] Recent studies have shown that intereye differences in RNFL and GCIPL can accurately diagnose previous cases of unilateral optic neuritis.[31,35,36] In addition, MOG-IgG-related optic neuritis has been shown to result in relative preservation of the GCIPL, whereas AQP4-IgG-related optic neuritis results in significant GCIPL loss.[37,38] These findings suggest that OCT may have a role in diagnosing these patients when they are seen after the acute period. The various causes of optic neuritis, however, have overlapping features that preclude OCT from being clinically useful alone at this time.

NMOSD is characterized by optic neuritis, longitudinally extensive transverse myelitis in the spinal cord, and brain stem encephalitis.[39,40] NMOSD shares many similarities with MS, such as presenting with optic neuritis, but carries distinct immunopathogenesis.[39,40] The majority of patients with NMOSD have detectable AQP-4 or MOG antibodies, which assists in making the diagnosis.[39] The optic neuritis associated with NMOSD often has atypical features such as being recurrent, bilateral, and more severe.[39,40] Hence, while many of the OCT changes described in idiopathic or MS-related optic neuritis will also be seen in NMOSD, recurrent episodes of optic neuritis in NMOSD can result in severe optic nerve atrophy with RNFL values <30 μm and flooring effects of the RNFL and GCIPL.[41] Bilateral OCT changes are often seen due to involvement of the optic nerve near the chiasm which can result in carryover effects.[39,42] The presence of microcystic macular edema on OCT is more prevalent in patients with NMOSD (20%–26%), even more so in those with the AQP-4 positive phenotype (40%) relative to MS patients (5%), although this feature can be seen in other optic neuropathies.[41,43] These features on OCT can help differentiate from

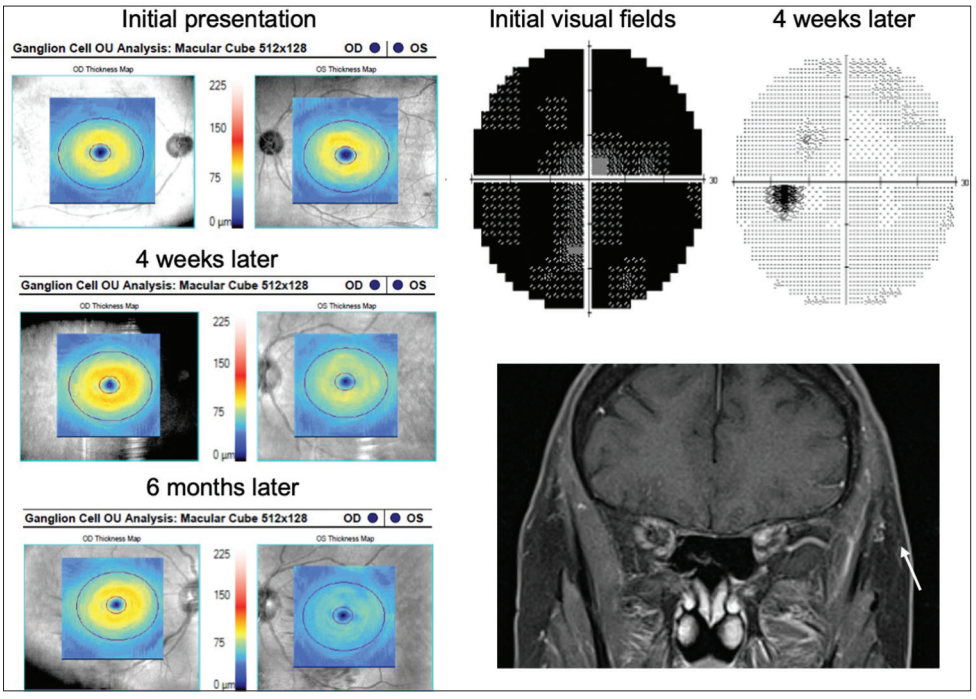

Figure 2: Left idiopathic optic neuritis. Initial visual fields were diffusely depressed with full recovery after 4 weeks. However, on optical coherence tomography, early ganglion cell–inner plexiform layer thinning is seen. Despite visual field improvement, there was significant ganglion cell–inner plexiform layer thinning at 6 months

NMOSD from other demyelinating optic neuropathies, which has historically been difficult to do.

Diagnosis of MS is based on the MacDonald criteria, which requires dissemination in time (DIT) and dissemination in space (DIS) for diagnosis.[44] The optic nerve is not currently a lesion site listed in the 2017 revisions to the MacDonald criteria despite a high prevalence of acute optic neuritis in MS.[44,45] This criteria did not use OCT testing and acknowledged that further studies using OCT to prove DIS would be helpful.[44] Since then, studies have shown that inclusion of asymptomatic patients with optic nerve lesions to satisfy DIS can improve sensitivity of the MacDonald criteria while maintaining specificity.[46] Studies have shown that RNFL thickness can be used as a clinical biomarker of visual function, response to disease-modifying therapies, and overall disease progression in MS.[47,48]

Increasingly, there is an emphasis on axonal loss being a main contributor to permanent disability in progressive forms of MS.[49] Magnetic resonance imaging (MRI) is limited in its specificity to detect axonal loss, and use of OCT to quantify retinal layers is likely the most accessible way to determine axonal loss in MS patients. Recent work has shown thinning of the RNFL and GCIPL on OCT as a marker of MS disease activity independent of optic neuritis.[32] The thinning is known to be dependent on the duration of disease, showing the greatest effect in early disease with a plateau effect.[50] Thinning of the RNFL in MS has also been associated with worse functional outcomes and decreased quality of life.[51] These data suggest that OCT changes could reflect global axonal loss and that neuroprotective interventions may have the most impact early in the disease. This is supported by the observation that RNFL and GCIPL atrophy were faster in progressive MS compared to relapsing–remitting MS.[52]

There is increasing interest in the volume of the inner nuclear layer (INL) as a marker of central nervous system (CNS) inflammatory disease activity. The INL is deep to the GCIPL and is a network of bipolar, amacrine, and horizontal cells.[32] The INL is not subject to retrograde degeneration nor does it thin in optic neuritis. The mechanism of INL thickening in MS optic neuritis is still being studied, but is postulated to be due to dynamic fluid shifts from adjacent vascular plexuses.[30] A study of disease-modifying therapies in MS showed a reduction with INL volume that correlated with therapeutic activity and overall CNS inflammation.[53] Future directions may look at how the INL volume changes during the acute phases of optic neuritis and how it correlates with radiological signs of inflammatory activity in MS.

OCT-A has been used to study optic neuritis despite ischemia or changes in circulation not being the primary etiology.[19] The ONH flow index, a marker of radial peripapillary capillary (RPC) circulation, was significantly lower in patients with a history of optic neuritis compared to healthy controls.[54] Reduction in RPC circulation in optic neuropathies of a nonischemic etiology may simply be related to the reduction in the retinal nerve fiber and GCLs.[19]

Nonarteritic anterior ischemic optic neuropathy

While there are no diagnostic features of NAION on OCT, both spectral-domain (SD) OCT and more recently OCT-A have demonstrated utility in monitoring disease course through the acute and postacute phases.[55,56] Segmentation of the RNFL using SD-OCT in acute NAION is limited by edema, and studies have suggested that GCIPL thinning is a better indicator of visual impairment.[57] GCIPL thinning was present within the 1st month following acute NAION and was found to precede reliable RNFL changes which can take months.[57] NAION has also been found to have characteristic "altitudinal" changes of the GCIPL, where the one horizontal hemisphere thins greater than the other, which has been used to differentiate it from optic neuritis at 2 weeks post-onset [Figure 3].[58,59] After an initial episode of NAION, patients are known to be at an increased risk of developing NAION in the fellow unaffected eye.[56] A study by Duman *et al*. compared fellow unaffected eyes to controls using SD-OCT and found subclinical retinal changes, specifically mean GCIPL thinning and RNFL thinning in the superior and nasal quadrants.[51] The exact pathogenesis of NAION is not known, but the leading hypothesis relates to impairment of perfusion to the ONH via the short posterior ciliary arteries. OCT-A has increasingly become a useful tool in NAION by advancing our understanding of its pathophysiology and prediction of functional outcomes. Multiple recent studies of OCT-A in NAION have established a structure–function relationship, demonstrating that bidirectional changes in the vascular flow density of superficial capillaries surrounding the ONH are positively correlated with a degree of visual improvement.[55,60,61] OCT-A has also been used to differentiate NAION from unaffected eyes or other forms of optic disc edema, such as optic neuritis and papilledema, with NAION having a significantly lower peripapillary vessel density.[62,63]

Papilledema

Papilledema has been characterized on OCT by the elevation of the peripapillary RNFL, which obscures the optic disc margins on fundoscopy and is seen in idiopathic intracranial hypertension (IIH). OCT has shown utility in differentiating papilledema and pseudopapilledema, an anomalous elevation of the optic disc, through its ability to identify edema within the nerve fiber layers, presence of vitreous traction, and visualization of deep ODD using

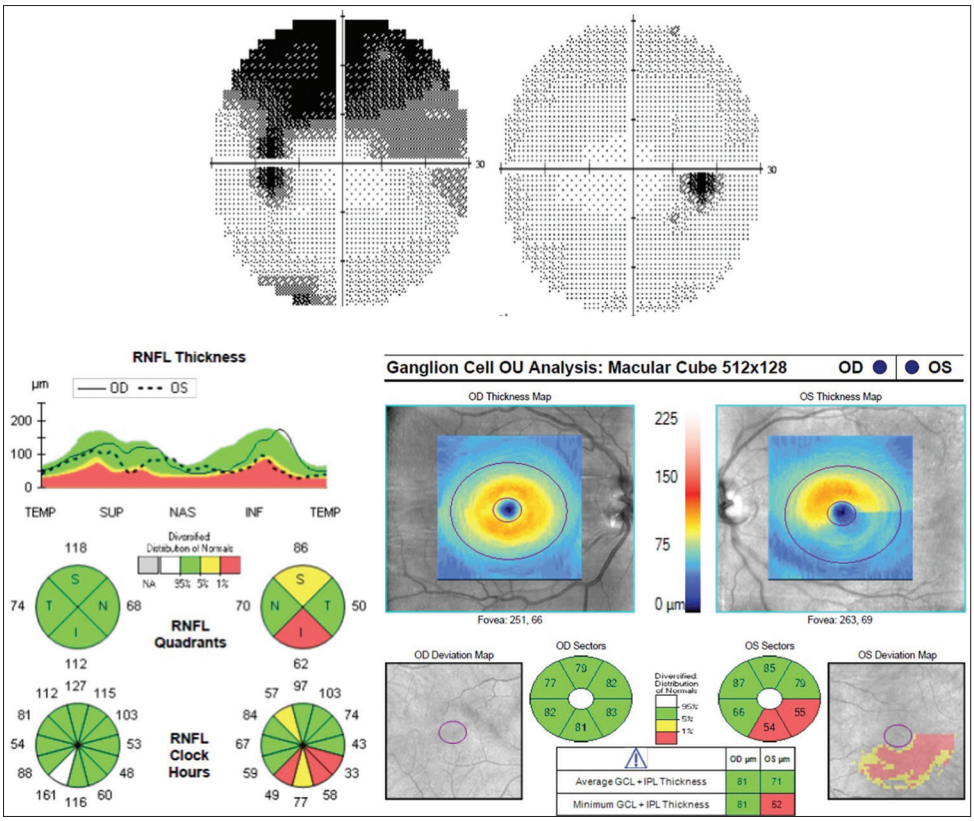

Figure 3: Left nonarteritic anterior ischemic optic neuropathy with typical arcuate visual field loss. Optical coherence tomography shows mostly inferior retinal nerve fiber and the ganglion cell–inner plexiform layer thinning both corresponding to the visual field loss

EDI-OCT.[64] Quantification of retinal layer volumes with OCT has shown that patients with papilledema have larger outer macular RNFL ring volumes in the inferior and nasal quadrants, while the macular GCIPL shows loss in the outer temporal region.[64] These OCT changes are similar to patterns seen in glaucoma where a pressure gradient also exists across the lamina cribrosa, leading to stasis of axoplasmic flow.[64,65] In addition to the diagnosis of papilledema and IIH, OCT has also been shown to predict visual outcomes through quantification of the GCIPL. Thinning of the GCIPL measured in the initial months following IIH diagnosis was correlated with poor visual outcomes at 1-year follow-up and preceded detectable visual field changes.[66,67] Other studies have suggested that in addition to single values, early changes in GCIPL thickness following diagnosis of IIH, specifically thinning >10 μm in the first 2–3 weeks following diagnosis, are also correlated with poor visual outcomes.[68] Papilledema also results in retinal changes outside of the optic nerve including submacular fluid, choroidal neovascular membranes, and choroidal and retinal folds, which may be difficult to appreciate on clinical examination and can be better assessed with OCT [Figure 4].[69] This can help explain reduced central visual acuity or visual field defects that may not be directly attributable to papilledema.

OCT is also being used as a noninvasive method of monitoring changes in ICP and response to treatment for underlying causes of papilledema. The shape of the peripapillary retinal pigment epithelium and/or Bruch's membrane (pRPE/BM) seen on OCT can often be anteriorly displaced due to the translaminar pressure differences in increased ICP.[70,71] Reduction in the anterior displacement of the pRPE/BM was associated with better treatment outcomes in IIH.[72] Future directions include improvement of techniques to efficiently and accurately label the BM as the edges can often be obscured by disc edema.[72] A recent pilot study showed that *en face* OCT could be used to monitor papilledema as objective parameters such as diameter of edema and subjective ranking by neuro-ophthalmologists were well correlated with RNFL thickness in patients being treated for IIH.[73] There have been advancements in the software used in OCT-A to quantify the vessels and demonstrated a decrease in ONH capillary density in both NAION and papilledema.[55,74] Peripapillary vessel density seen on OCT-A has also been shown to be correlated with grading of papilledema and may also have potential as a clinical marker of early optic nerve damage due to correlations found with choroidal blood flow and GCL thickness.[75]

Toxic and nutritional deficiencies optic neuropathies

Optic neuropathies can be secondary to toxic effects of medications or tobacco and nutritional deficiencies such as Vitamin B12. Ethambutol, an antituberculosis drug, is a well-established cause of severe toxic optic neuropathy that is often irreversible even with immediate discontinuation of the medication.[76] However, early stage ethambutol optic neuropathy (EON) is often associated with a normal appearing fundus.[77] OCT has been used in retrospective studies to identify subclinical early EON through both increases and decreases in RNFL thickness.[78,79] A recent study found that GCIPL changes preceded fundus abnormalities and thinning was negatively correlated with a degree of visual recovery.[80] GCIPL changes after discontinuation of ethambutol could be used to predict recovery at 12 months after stoppage.[80] There is likely value in regular screening and clinical investigation of the RNFL and GCIPL after initiation of ethambutol treatment.[78] Optic neuropathies and RNFL thickening are a relatively rare, but potentially the only, manifestation of nutritional deficiencies such as thiamine.[81] In general, it has been described that OCT of nutritional and toxic optic neuropathies presents with thinning of the temporal RNFL and diffuse GCIPL thinning with central field loss [Figure 5].[82] The former of which has been suggested to be related to Wallerian degeneration and preferential effects on the papillomacular fibers.[83,84] These studies suggest that a multimodal imaging approach, including OCT, is useful in the potential early identification and confirmation of optic neuropathies related to nutritional deficiencies or adverse drug reactions.

Hereditary optic neuropathies

Hereditary optic neuropathies are caused by inherited nuclear or mitochondrial DNA point mutations which affect cellular metabolism and may present at any point in life. Leber's hereditary optic neuropathy (LHON) is a rare condition resulting in bilateral optic neuropathies which have typically been characterized on OCT with initial thickening of the RNFL and choroid followed by thinning.[2] Choroidal remodeling and vascular changes seen in chronic LHON have led to recent studies using SS-OCT to better visualize the GCIPL and deep choroidal structures with better spatial resolution.[85] Thinning of the GCIPL has been found to precede RNFL swelling in acute LHON and provides a more sensitive marker of disease progression in known disease carriers.[85-87] Dominant optic atrophy (DOA) is similar to LHON, but typically presents earlier in life with a slow, progressive loss of vision. While the natural history of LHON and DOA is quite different, these conditions can sometimes have overlapping features. OCT has demonstrated that DOA shows RNFL thinning in the superior and inferior quadrants, whereas LHON has RNFL thickening in the acute stage, consistent with what is clinically observed.[86]

Compressive Optic Neuropathies and the Optic Chiasm

Compressive optic neuropathies typically present with slowly progressive, painless vision loss, and etiologies include pituitary macroadenomas, craniopharyngiomas, and aneurysms.[2] Chronic compression of the optic chiasm resulting in a bitemporal hemianopia shows characteristic RNFL fiber loss on OCT that has been coined "bow-tie atrophy."[2] This comes from the arcuate radiations of the slightly nasally positioned optic disc.

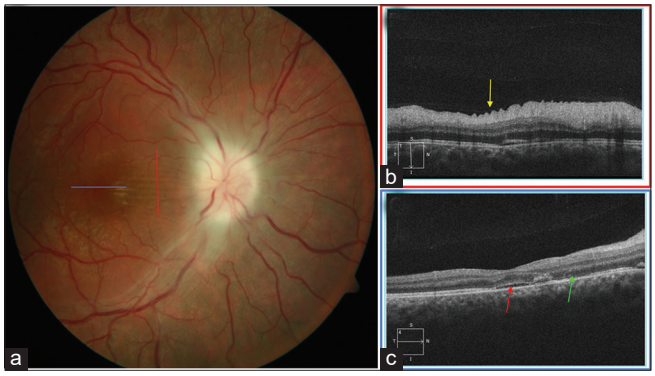

Figure 4: Optic atrophy from papilledema. (a) Vertical raster optical coherence tomography scan (red line) highlights the (b) radial retinal folds (yellow arrow). (c) Horizontal raster optical coherence tomography scan through the fovea demonstrates mild subretinal fluid (red arrow) and dropout of the ellipsoid zone (green arrow)

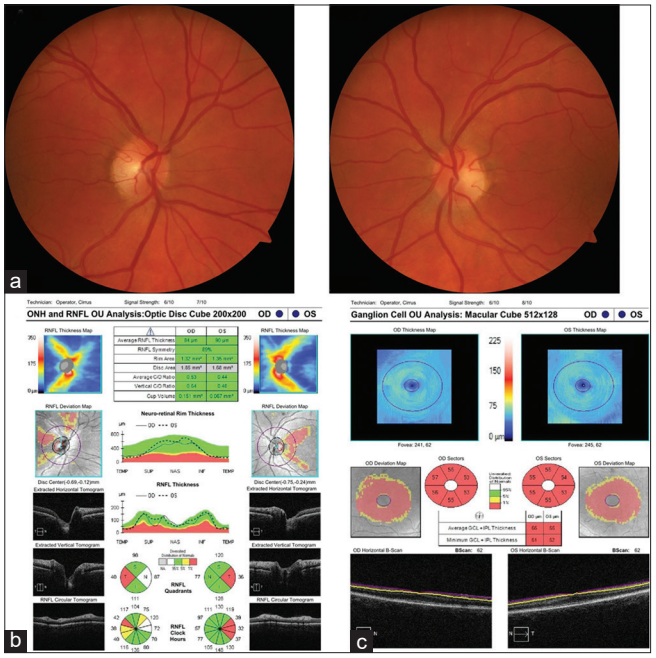

Figure 5: Vitamin B12 deficiency optic neuropathy. (a) Fundus photographs demonstrated temporal pallor of the optic nerves. (b) Optical coherence tomography showed temporal retinal nerve fiber layer thinning. (c) Optical coherence tomography of the ganglion cell–inner plexiform layer showed diffuse thinning

A similar pattern can also be seen in OCT-A where loss of the superficial retinal capillary network can be seen in the areas of classic bow-tie atrophy.[88] On the other hand, atrophy of the GCIPL in chiasmal lesions affecting nasal optic fibers typically respects the vertical meridian of the retina and can be more easily correlated with visual field loss [Figure 6]. Suprasellar masses may also affect the anterior optic chiasm resulting on a junctional scotoma or the optic tract, producing a homonymous hemianopia and corresponding OCT GCIPL changes [Figures 7 and 8]. Visualization of GCIPL atrophy using OCT is important as it is a predictor of worse visual prognosis after surgical decompression.[89]

OCT assessment of RNFL and GCIPL thicknesses is recommended in the preoperative evaluation of patients with sellar/suprasellar masses.[90] Earlier studies using OCT in this context focused mainly on RNFL thickness.[91,92] More recent evidence has suggested that the GCIPL is also important in evaluating compressive chiasmal lesions.[93,94] This is particularly true in early or mild chiasmal compression where distinct patterns of binasal GCIPL thinning were seen even before the RNFL.[93,95] Thinning of the GCIPL may be the first sign of early chiasmal compression affecting the anterior visual pathways and can be present in the absence of visual field deficits or compression on MRI.[95] In addition to the GCIPL, recent studies in patients with pituitary tumors have also shown that nasal and temporal RNFL thinning can occur in chiasmal compression without visual field loss.[96]

Preservation of RNFL and GCIPL thickness prior to medical or surgical treatment has been shown to be predictive of visual recovery.[92] The mechanism of recovery includes initial removal of the conduction block due to the compression, secondary remyelination, followed by restoration of axoplasmic flow.[2] Early or chronic cases of mild compression causing only a conduction block without atrophy of the ganglion cells are thus more likely to make a faster and more complete recovery. In patients with suprasellar tumors, normal thickness of the RNFL (≥70 μm) preoperatively was found to be the only significant predictor of improved postoperative visual acuity and fields among other non-OCT clinical characteristics in a multivariate analysis.[97] Recent studies have used preoperative inferior and superior RNFL thickness as part of a risk prediction model that accurately prognosticates long-term visual recovery and maintenance following pituitary tumor surgery.[98] While many patients show persistent GCIPL loss even after visual recovery, thickness of the GCIPL was positively correlated with post-operative visual field outcomes.[93] Similar findings have been replicated in thyroid eye disease looking at RNFL thickness as a predictor of surgical outcomes in individuals with significant visual field defects due to compressive optic neuropathy.[99] There is emerging evidence to suggest in some cases that nasal GCIPL thickness may have superior prognostic power to the RNFL in postoperative visual outcomes in sellar tumours.[100]

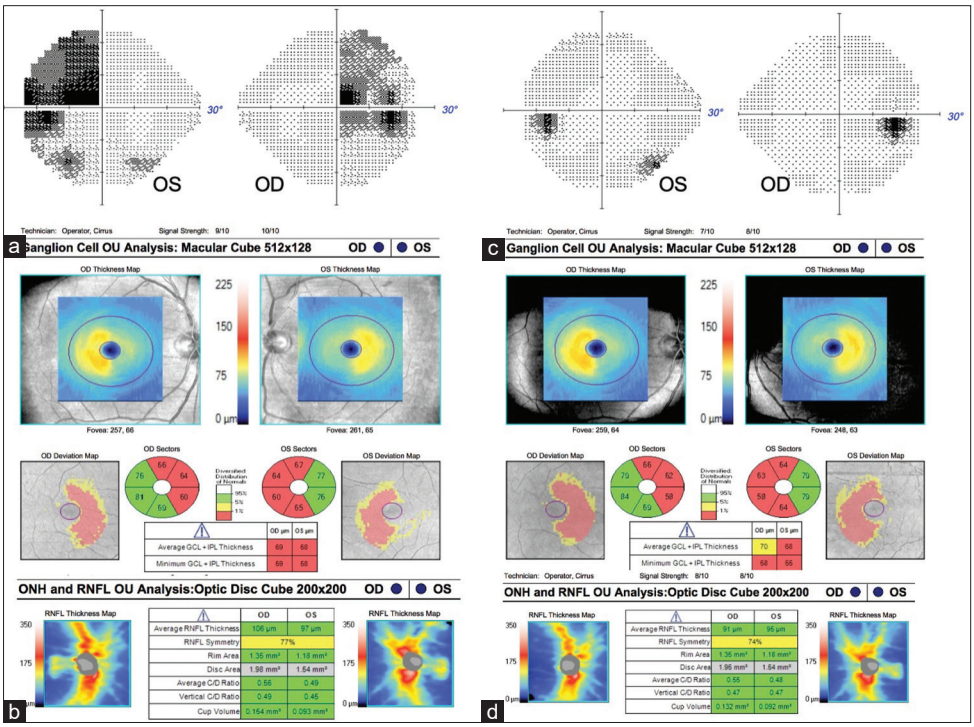

Figure 6: Bitemporal hemianopia secondary to prolactinoma. (a) Optical coherence tomography of the ganglion cell–inner plexiform layer showing binasal thinning while the (b) retinal nerve fiber layer showing temporal thinning. (c) After medical treatment, the visual field defect resolved, but (d) the binasal ganglion cell–inner plexiform layer thinning persisted

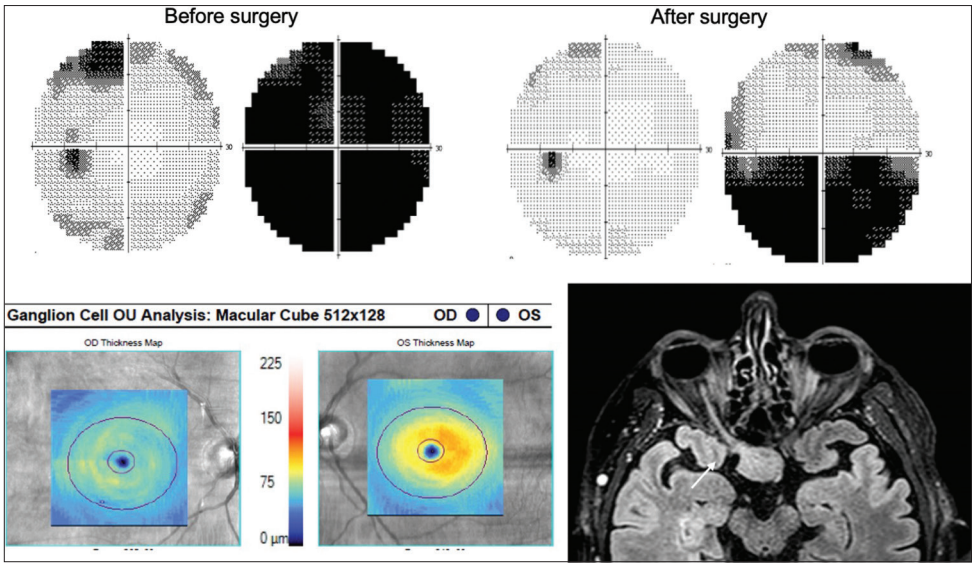

Figure 7: Pituitary macroadenoma causing a right junctional scotoma. Corresponding ganglion cell–inner plexiform layer thinning is seen on optical coherence tomography. There was some recovery of visual field loss in the right eye and full recovery in the left after surgery

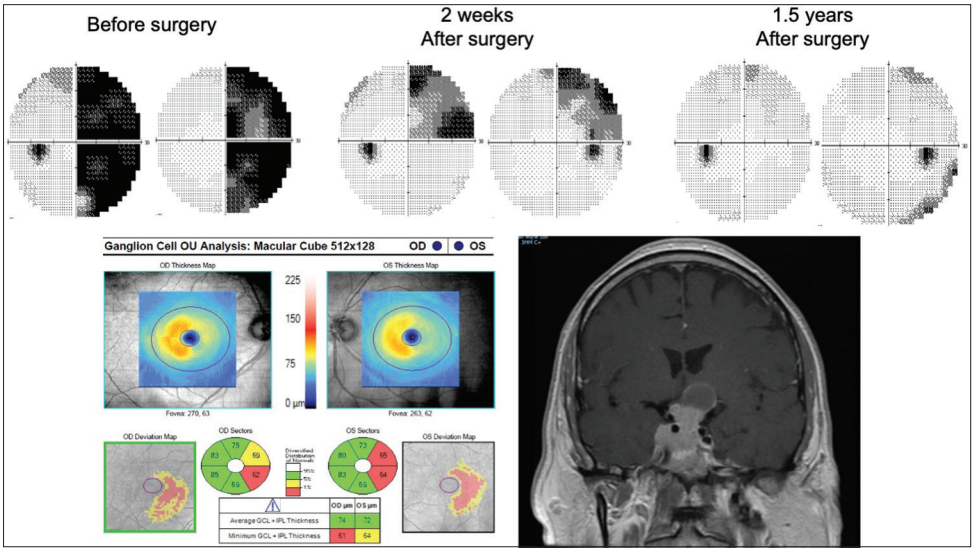

Figure 8: Pituitary macroadenoma extending into the cavernous sinus and left optic tract. Prior to surgery, there was a right homonymous visual field loss and corresponding ganglion cell–inner plexiform layer loss on optical coherence tomography. After surgery, he regained vision despite persistent corresponding ganglion cell–inner plexiform layer loss

It should be noted that changes in the RNFL and GCIPL on OCT are not always seen, particularly in the case of chronic chiasmal compression.[101] However, preserved RNFL and GCIPL in the case of chronic chiasmal compression seem to suggest good visual prognosis adding to its value as a predictor of visual recovery.[101] Since optic disc pallor is a subjective sign that is open to interpretation, RNFL and GCIPL thickness provides an objective measure that can easily be documented and compared at each visit and can be more reliable than visual field testing.[102]

Retrochiasmal Visual Pathways

Recent studies in the use of OCT in retrochiasmal lesions have looked at the temporal evolution, morphology, and frequency of GCIPL thinning in patients with homonymous hemianopia and retrochiasmal lesions.[103] In contrast to RNFL thinning which produces "bow-tie" atrophy in the contralateral eye, Mühlemann *et al*. proposed referring to the pattern of GCIPL thinning as homonymous hemiatrophy to illustrate its respect for vertical meridian.[98] Within the retrochiasmal pathway, lesions can further be classified relative to where the retinal ganglion cells synapse at lateral geniculate nucleus, either pregeniculate or postgeniculate.[103] Atrophy of RNFL and GCIPL still occurs even in postgeniculate lesions despite no direct lesions to the axon and is due to retrograde transsynaptic degeneration (RTSD).[104] GCIPL thinning was found to have higher sensitivity for detecting RTSD and occurs earlier after lesion onset compared to RNFL thinning.[103]

However, analyses using a combination of RNFL and GCIPL thinning were superior to either layer on its own.[103]

Previous studies have found that RNFL thinning can be detected immediately for pre-geniculate lesions whereas this process takes longer for post-geniculate lesions, being first detectable at approximately 5 months.[103] Additionally, there is recent evidence to suggest that GPICL thinning in post-geniculate lesions may occur in a biphasic fashion, in contrast to previous studies that reported an exponential decline.[103] Other studies have also found GCIPL homonymous hemiatrophy in patients without detectable visual field deficits suggestive of retrochiasmal lesions.[105] In a case series, these GCIPL changes were due to demyelinating processes with resolved visual field deficits and remote traumatic brain injury.[106] These data suggest that homonymous hemiatrophy of the GCIPL could be used as a tool for documenting previous lesions to the retrochiasmal visual pathways and be helpful for establishing DIT or DIS. Similar to chiasmal lesions, homonymous hemiatrophy of the GCIPL on OCT may be the first sign that a neoplastic lesion is affecting the retrochiasmal visual pathways.[107]

Optical Coherence Tomography and Neurodegenerative Disease

The ability to quantify the RNFL and GCIPL using OCT is being studied as a noninvasive means of evaluating neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). A meta-analysis found that the GCIPL, RNFL, and choroid were all thinner in individuals with AD.[108] These findings support the hypothesis that AD affects both cerebral neurons and the ganglion cells of the retina.[108] While a similar trend was found in individuals with mild cognitive impairment (MCI), often a precursor to AD, this effect did not reach statistical significance.[108] However, a study in amyloid-proven AD cases only found an association with macular thinning, not the RNFL.[109] Another study in "preclinical AD," defined as cognitively normal individuals with amyloid pathology on positron emission tomography, also found no association with RNFL thinning.[110] A cross-sectional study of seniors without AD found that changes in GCIPL were associated with decreased global cognition and may represent an early marker of progression to AD.[111] Future studies could confirm the findings that suggest that GCIPL thinning is more prevalent compared to RNFL thinning in conditions thought to precede AD. Involvement of the RNFL and GCIPL could be due to pathological cerebral changes similar to retrochiasmal lesions, leading to RTSD or direct neurotoxic effects to the retina. Involvement of the choroid could be explained by cerebral vascular impairment, being one of the earliest features of AD and deposition of amyloid-beta could occur in the choroidal vasculature.[112] The theory of vascular impairment is also supported by OCT-A studies that showed significant changes in macular vessel and perfusion density in AD compared to MCI and controls. Future directions may include prospective studies to understand how OCT changes may predate cognitive changes and its temporal relationship to development of AD. Longitudinal studies could also be more sensitive to subtle changes over time and reduce the effect of interindividual differences.[109]

There is also interest in the use of OCT in patients with parkinsonism, which can be separated into PD and atypical parkinsonism such as progressive supranuclear palsy (PSP). Retinal ganglion cells are known to in part use dopaminergic transmission to modulate visual processing.[113] Parkinsonism is the result of decreased dopaminergic transmission in the basal ganglia. It is thought that the various mechanisms that reduce dopaminergic transmission in the basal ganglia can also affect the retina.[113] Therefore it is speculated that retinal changes measured by OCT could be used as a surrogate marker of progression in conditions such as Parkinson's disease.[113] OCT changes consistent with nonspecific neurodegeneration such as RNFL and macular thinning have long been described in patients with PD.[114] Recent work has focused on looking at OCT changes seen in those with rapid eye movement sleep behavior disorders (RBD) as a surrogate for prodromal PD and have seen RNFL and GCIPL thinning in these individuals.[115,116] Other studies have found different patterns of RNFL thinning on OCT when comparing different forms of parkinsonism such as PSP.[117] However, at this time, many of the changes described are also seen in general neurodegeneration, thus limiting the clinical use of OCT in the prediction or evaluation of parkinsonism. Future work could involve longitudinal studies to determine if OCT could be used as a screening tool in RBD patients to predict progression to parkinsonism.

Conclusions

OCT has become an important tool in the evaluation of neuro-ophthalmologic diseases of the afferent visual pathway through its ability to directly visualize and quantify retinal tissues such as the RNFL and GCIPL. Recent work in the use of OCT has included the localization of lesions in the afferent visual system based on patterns of RNFL and GCIPL thinning such as in compressive chiasmal and retrochiasmal lesions. OCT has shown that patients with transient autoimmune or inflammatory lesions of the optic nerve can have lasting changes on OCT that can be used reliably to detect previous episodes of optic neuritis or retrochiasmal lesions. Moving forward, OCT may be formally included in the diagnostic criteria of MS as one tool to demonstrate dissemination of

demyelination in space and time. The utility of OCT is also expanding beyond ophthalmology to other specialties such as neurosurgery and neurology to help prognosticate diseases with specific manifestations in the visual system such as pituitary tumors or as a surrogate marker of more global neurodegeneration as seen in AD. The scope of OCT is likely to continue to expand and will be an increasingly important aspect in assessing neuro-ophthalmologic disease moving forward.

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Conflicts of interest

The authors declared that there are no conflicts of interests of this paper.

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