LEARNING OBJECTIVES

The attendee will be able to:

1. Understand OCT as it applies to optic neuropathy-related neurologic diseases such as MS.
2. Understand OCT applications to CNS diseases associated with disc edema.
3. Understand relationships between OCT measures and other CNS measures including clinical optic nerve function.

CME QUESTIONS

1. OCT works by:
   a. light reflectivity
   b. echo location
   c. birefringence of the retinal axons
   d. xray imaging
   e. magnetic imaging

2. OCT has demonstrated retinal nerve fiber loss in which of the following conditions:
   a. optic neuritis
   b. MS
   c. Alzheimer’s disease
   d. NAION
   e. All of the above

3. OCT is an emerging non-invasive technology that at present is a useful tool in the GROUP analysis of neuro-ophthalmic conditions, rather than the basis for INDIVIDUAL clinical decisions. True or False

KEY WORDS

1. OCT
2. Optic Neuritis
3. Multiple Sclerosis
4. Papilledema

INTRODUCTION

Optical coherence tomography (OCT) has evolved dramatically since the first reports of this technology in 1991, and has become an integral part of the ophthalmology evaluation. In addition to providing an indispensable service for the retina physician, the ability to quantify the retinal nerve fiber layer has begun to change neuro-ophthalmic practice. In this regard, OCT has the potential to change qualitative, subjective descriptive reporting into reproducible quantitative science.

Quantification of the RNFL has several clinical applications, including numerous diseases of the optic nerve, both in documentation of edema and quantification of optic atrophy; OCT has also become a viable study outcome in treatment trials. This review will focus on current OCT applications as they apply to neuro-ophthalmic clinical practice.

RETINAL IMAGING METHODOLOGIES

In addition to OCT, commercially available retinal imaging devises also include Heidelberg Retinal Tomography (HRT), and scanning laser polarimetry (GDx). Each of these instruments has inherent advantages and disadvantages, and results obtained from 1 instrument do not translate into results from another imaging technique. The Heidelberg Retina Tomograph (HRT) is a confocal laser scanning system to acquisition three dimensional retinal images. GDx relies on birefringence of the retinal ganglion cell axon microtubules and filaments. Monteiro and Moura compared GDx with variable corneal compensation (VCC) against TD-OCT in patients with band atrophy (BA) from chiasmal compression, and reported GDx appeared to underestimated the temporal quadrant by an average of 22µm; conversely, Zaveri et al found OCT and GDx-VCC equally able to measure RNFL thickness in MS patients experiencing acute optic neuritis; by virtues of assessing retinal ganglion cell axon microtubule density, GDx changes appeared earlier than OCT-demonstrable RNFL thinning. The remainder of this review will focus on OCT as the most common methodology employed in neuro-ophthalmic practice.

OCT METHODOLOGY

Time-domain OCT (TD-OCT), the 3rd generation instrument, is able to record a series of 512 x 1024 A-scan images within 2 seconds with approximately 10µm resolution. Several studies have demonstrated TD-OCT’s reproducibility in assessing the RNFL thickness in normal eyes, glaucoma, and various non-glaucomatous optic
neuropathies. The next generation of OCT, Spectral-domain OCT (SD-OCT), has significantly improved the speed of image acquisition; the SD-OCT captures approximately 27,000 scans per second with a resolution of 5µm, and has the ability to form a 3-dimensional map of the retina and optic nerve, allowing more accurate distinctions between retinal layers. In addition, SD-OCT automatically centers the scan on the optic disc with the use of optic nerve landmarks to decrease scan — rescan variability. Although measurements with the TD-OCT and SD-OCT instruments correlate well, the RNFL and retinal thickness results are not interchangeable.

OCT VS Histology
Blumenthal et al compared OCT-derived RNFL measurements to histology-derived measurements (exenterated orbit secondary to an infiltrative squamous cell carcinoma), and reported OCT outcomes mirrored the histology, but actual measurements differed by 10–40µm. This discrepancy likely reflects identification of the RNFL layers via staining techniques versus optical reflectance.

FACTORS INFLUENCING SCAN ACCURACY
Several factors influence the quality of OCT images. The 3.4 mm laser reticule must be centered on the optic nerve; decentered scans preferentially affect quadrant thicknesses, especially the vertical quadrants, while total RNFL remains relatively stable. Surprisingly, use of the OCT scan tracking coordinates only provided a statistically significant effect on the temporal quadrant. Signal strength also positively correlates with the observed RNFL thickness; many studies require signal strength of 7. Pupil size is not generally a significant factor as long as size is ≥ 3mm. Lens opacities are inversely correlated with the measurement of RNFL thickness (effect size <12%); similarly, contact lenses use is associated with decrease in signal strength (7.8 to 7.1; P=0.011) and the measured average RNFL thickness (average RNFL 105.3 to 102.8µm; P=0.001).

OCT IN CNS DISEASE/OPTIC NEUROPATHIES
Anterior Ischemic Optic Neuropathy (AION)
AION is a disease characterized by disc edema at onset with subsequent optic atrophy. Contreras and colleagues used OCT to study 27 patients with NAION at baseline, 6–weeks; and 3, 6, and 12 months after onset. The initial mean RNFL of 201µm represented a 96.4% increase relative to the fellow eye. Percentages of RNFL loss 3, 6, and 12 months after onset were 38.9%, 42.3%, and 43.9%, respectively. Regression analysis revealed a 2–dB decrease in visual field function for every 1–µm of mean RNFL thickness loss, and a 1-line drop in Snellen visual acuity for every 1.6µm deficit.

Bellusci et al documented RNFL edema followed by thinning in the superior optic nerve among acute NAION patients with inferior altitudinal defects; conversely, patient with diffuse visual field (VF) loss had extensive RNFL thinning. Temporal quadrant RNFL thinning (papillomacular fibers) correlated with central field defects. Chan et al used OCT to investigate the optic disc in 22 NAION patients; smaller cups and C:D ratios were more common in NAION eyes compared to control eyes; additionally, a smaller cup was present in the non–affected fellow eye of NAION patients (C:D 0.103) compared to the affected NAION eye (C:D 0.135; P=0.04), suggesting a small degree of cup enlargement after NAION.

These studies indicate that OCT–measured RNFL values correlate with the topographical representation of visual field defects in eyes with NAION. Further, reduced RNFL values can help predict recovered visual function in NAION patients.

Optic Neuritis (ON) & Multiple Sclerosis (MS)
Several investigators have demonstrated RNFL loss in MS patients even without a history of optic neuritis, while superimposed optic neuritis produces additional RNFL decline. There is a clinical–OCT paradox concerning optic neuritis, similar to the MRI-clinical paradox within MS. MRI T2 lesion load does not correlate with overall neurologic function, with MS patients often exhibiting MRI lesions out of proportion to their clinical condition (especially as assessed by the EDSS). Similarly, OCT RNFL loss appears out of proportion to the clinical visual assessments. Although the majority of patients lose RNFL following an episode of optic neuritis, most recover “normal” visual function (despite the patients’ perception that the ‘recovered’ eye is not normal). Costello et al documented an OCT injury threshold of 75µm before a linear decline in visual field was apparent. Several studies have investigated RNFL quadrant data after optic neuritis, and there appears to be a predilection for the infero–temporal quadrants.

Costello et al investigated OCT findings in CIS optic neuritis. There was no significant difference in RNFL thickness between CIS progressing to MS versus CIS without MS at 2 years follow up; however, progressive RNFL thinning was more apparent in CIS patients progressing to MS.

OCT has been used to investigate MS subtypes; RNFL loss is generally greater in progressive MS than RRMS (somewhat duration of disease dependent).

Neuromyelitis Optica (NMO)
In most reports, NMO is associated with greater RNFL loss than optic neuritis or MS. De Seze et al reported RNFL thickness of 29 NMO patients had significantly reduced RNFL values (77.9 µm) compared to controls. OCT is not specific enough to distinguish NMO form ON/MS, but NMO should be considered in ON patients with poor recovery, or dramatic RNFL thinning <50µm.
Papilledema/Pseudotumor Cerebri (PTC)/Idiopathic Intracranial Hypertension (IIH)

Patients with idiopathic intracranial hypertension (IIH) typically present with headache, pulsatile tinnitus, transient visual obscurations, and papilledema usually with relatively preserved visual acuity.

Intuitively, we expect elevated RNFL values at presentation when optic disc edema is maximal, and decreasing RNFL elevation with effective treatment.

Rebolleda and Munoz-Negrete studied 22 PTC patients, and noted the initial increase in RNFL correlated well with visual field mean deviation (MD) (P=0.002) and pattern standard deviation (PSD; P=0.013). At 1 year follow-up, perimetry demonstrated a 0.6dB MD decline with a 10μm RNFL decrease. It should be noted that OCT alone is unable to distinguish resolving edema from emerging optic atrophy, and therefore OCT needs to be incorporated into the remainder of the clinical exam. Additional information on OCT in IIH will emerge from the OCT substudy of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Optic Nerve Head Drusen

Johnson et al applied the TD-OCT “fast optic disc” protocol to differentiate disc drusen from disc edema. Drusen appeared more “lumpy-bumpy” with RNFL thinner than 86μm nasally in contrast to the smooth and elevated contour of true disc edema.

Compressive Optic Neuropathy (CON)

Danesh-Meyer et al investigated OCT’s ability to predict visual recovery from CON. Thirty five patients with various etiologies of CON were evaluated with OCT and visual fields pre- and post-surgical decompression. The patients were divided into 2 groups: “normal” RNFL and “thin” RNFL (defined as pre-op RNFL <97.5% of normal values). Patients with reduced VA and VF but normal RNFL thickness had significant improvement of VA (mean of 20/40 to 20/25; P=0.028) post-decompression than those with “thin” RNFL (20/80 to 20/60; P=0.177). Although the mean improvement in the “thin” RNFL group of 2 lines was statistically insignificant, this degree of improvement may well be clinically significant. The analysis found an increased likelihood of post-op improvement with a thicker pre-op RNFL until approximately 85μm, after which there was no additional benefit was observed; this likely reflects the fact that patients with RNFL of 85μm have relatively preserved visual function. While pre-op measurements of RNFL do not necessarily change our management of patients with CON, such studies enhance our ability to predict visual outcome post decompression in CON.

Hereditary Optic Neuropathies/Leber Hereditary Optic Neuropathy (LHON)

Leber hereditary optic neuropathy (LHON) is a mitochondrially inherited degeneration of retinal ganglion cells and their axons that leads to an acute or subacute loss of central vision. Affected patients are predominantly males, mutations in the mitochondrial genome from their mother. LHON is usually due to one of three pathogenic mitochondrial DNA (mtDNA) point mutations: at nucleotide positions 11778 G to A, 3460 G to A and 14484 T to C, respectively, in the ND4, ND1 and ND6 subunit genes of complex I of the oxidative phosphorylation chain in mitochondria. Clinically, patients may develop often acute onset visual loss in one eye, followed by fellow eye involvement months to weeks later. Vision loss typically occurs in young adulthood. In the acute stage, the affected eye demonstrates telangiectatic and tortuous peripapillary vessels; and with time, optic atrophy ensues.

Seo et al. studied RNFL in LHON patients with the 11778 and 14484 mutations. Patients were divided into early (≤6 months) and late (>6 months) categories. In the late stage, the RNFL thickness was greater in the 14484 group (average RNFL 81μm) compared to the 11778 (average RNFL 65.6μm; P=0.02), thus supporting severe atrophy in the late 11778 group. Comparisons between the 2 mutations in the early stage may be misleading, since there can be considerable variability within this time frame as thinning occurs. Overall, these OCT findings are in agreement with the clinical impression that the 11778 mutation is associated with worse visual outcome than the 14484 mutation.

Savini et al used OCT to study RNFL thickness in unaffected carriers with LHON mutations. Sixty-six unaffected carriers (44 females and 22 males) were analyzed and compared with an age–matched control group of 70 patients (40 females and 30 males). As compared to the control group, unaffected male carriers showed thicker RNFL measurements in the temporal and inferior RNFL quadrants and in the 360 degrees average measurements. These differences reached statistical significance in subjects carrying the 11778 mutation, whereas only a trend was detected in those with the 3460 mutation. Unaffected female carriers had an increased thickness in the temporal quadrant when compared with the control group (P = 0.003). The increase in temporal sectors was statistically significant in females with the 11778 mutation, whereas a trend was detected in those with the 3460 mutation. A thickening of the temporal fibers was detected in all subgroups of unaffected carriers.

Migraine

Martinez et al used OCT to study 70 patients with migraine, and noted a significant RNFL reduction in the temporal quadrants of migraineurs compared to healthy controls; additionally, the RNFL in migraine with aura (average RNFL 96.5μm) was significantly less than migraine without aura (average RNFL of 102.9μm; P=0.0189). Significantly thinner RNFL was found in patients with migraine ≥15 years. These investigators found a correlation between RNFL thickness and migraine disability assessment (MIDAS) scores.
Neurodegenerative disease/Alzheimer Disease
There is both histologic and retinal imaging evidence of retinal ganglionic cell (RGC) in patients with Alzheimer disease (AD). Danesh–Meyer et al used HRT scanning laser ophthalmoscopy (SLO) to investigate 40 patients with AD compared to age– and sex–matched controls, and found that clinical and SLO vertical cup–to–disc ratio was significantly different between the groups (AD 0.4, control 0.27–0.31); additionally, these authors reported decreased rim volume, RNFL thickness and rim area in AD compared to controls.

CONCLUSION
OCT has enhanced our assessment, management, and understanding of neuro–ophthalmic diseases, and has potential to further our understanding of other CNS–based diseases. OCT has the advantages of reproducibility, ease of use, non–invasive nature and relatively low cost, makes it an asset to several clinical situations. With its advancement into spectral domain, OCT has wide use in evaluating the optic nerve and the visual system.

CME ANSWERS
1. A
2. E
3. True

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