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To cite this article: Preeti Patil Chhablani, Vikas Ambiya, Akshay G. Nair, Sailaja Bondalapati & Jay Chhablani (2017): Retinal Findings on OCT in Systemic Conditions, Seminars in Ophthalmology, DOI: 10.1080/08820538.2017.1332233

To link to this article: http://dx.doi.org/10.1080/08820538.2017.1332233

Published online: 22 Jun 2017.
Retinal Findings on OCT in Systemic Conditions

Preeti Patil Chhablani¹, Vikas Ambiya¹, Akshay G. Nair¹, Sailaja Bondalapati², and Jay Chhablani¹

¹Srimati Kanuri Santhamma Centre for Vitreo Retinal Diseases, KAR Campus, L. V. Prasad Eye Institute, Hyderabad, Telangana, India and ²Duke University Hospital, Durham, NC, USA

ABSTRACT

Purpose: Imaging technology has advanced by leaps and bounds in the recent past and has resulted in a much greater understanding of ocular diseases. The aim of this review article is to summarize optical coherence tomography (OCT) findings of various systemic conditions.

Method: A systematic literature search of the Medline/PubMed database was performed. English articles up to April 2015 were included. Terms used for search included: Alzheimer’s Disease; Multiple Sclerosis; Parkinson’s Disease; Behçet’s Disease; Schizophrenia; Migraine; Obstructive Sleep Apnea Syndrome; Neurofibromatosis; Sickle Cell Disease; Renal diseases; Lupus Retinopathy; Valsalva Retinopathy; Whiplash Retinopathy; Shaken-Baby Syndrome; Choroidal metastases; Intracranial Hypertension; Drug toxicity; Deferoxamine; Sildenafil; Tamoxifen; Hydroxychloroquine; Chloroquine; Ethambutol; Lead; Sickle Cell Disease; and Thalassemia along with OCT.

Results: Studies have shown that inner retinal thinning could be the earliest sign of neurological diseases and may help to differentiate individuals with abnormalities. Outer retinal damage was noted in cancer-related retinopathy and secondary to drug toxicity as a diagnostic sign. This review article summarizes the OCT findings and their importance in early diagnosis, treatment, and follow-up in a varying spectrum of systemic diseases including neurological diseases, hematological diseases, cancer-related retinopathies, and systemic drug toxicity.

Conclusion: OCT findings are useful to predict the probability of a disease, to diagnose it early, to differentiate between healthy and unhealthy tissue, and to assess the effect of therapeutic interventions in many systemic diseases.

Keywords: Alzheimer’s disease, leukemia, lupus retinopathy, migraine, multiple sclerosis, obstructive sleep apnea syndrome, Parkinson’s disease, schizophrenia, shaken-baby syndrome, Sickle Cell disease

INTRODUCTION

Various systemic diseases affect eyes. The understanding of individual layers of the retina and choroid has been improved significantly with advanced imaging modalities. Optical coherence tomography (OCT) is now able to provide in-vivo histological images of the retina and choroid. There are multiple reports of OCT findings in systemic diseases ranging from neurological to blood dyscrasias. OCT findings have been reported to be beneficial in early diagnosis of neurological diseases as well as in understanding the visual prognosis with drug toxicity.

This review article summarizes the important and useful OCT findings of the retina reported in various systemic diseases and their clinical applications. Tables 1, 2, and 3 shows key OCT findings of systemic conditions.

Method of Literature Search

A systematic literature search of the Medline/PubMed database (www.ncbi.nlm.nih.gov/pubmed) was performed. English articles up to April 2015 were included. Terms used for search included: Alzheimer’s Disease; Multiple Sclerosis; Parkinson’s Disease; Behçet’s Disease; Schizophrenia; Migraine; Obstructive sleep apnea syndrome; Neurofibromatosis; Sickle Cell Disease; Renal diseases; Lupus Retinopathy; Valsalva Retinopathy; Whiplash Retinopathy; Shaken-Baby Syndrome; Choroidal metastases; Intracranial Hypertension; Drug toxicity; Deferoxamine; Sildenafil; Tamoxifen; Hydroxychloroquine; Chloroquine; Ethambutol; Lead; Sickle Cell Disease; and Thalassemia along with OCT.
NEUROLOGICAL DISEASES

Alzheimer’s Disease

Alzheimer’s Disease is a neurodegenerative disease characterized by progressive deterioration in cognition, behavior, and function. Accumulation of intracellular neurofibrillary tangles of hyperphosphorylated tau protein and extracellular amyloid β protein deposits (Aβ) trigger inflammation in the brain. This inflammation could cause thinning of the retinal ganglion layer, as the retina and brain share similar responses to inflammation.1 Such stress situations are particularly relevant to the exposed and metabolically sensitive retinal ganglion cells (RGC) and photoreceptor cells.

Earlier, Iseri et al. demonstrated a relationship between reduction in macular volume and the severity of cognitive impairment using time-domain OCT.2 Due to limitations of the device, changes in the individual layer were not possible to evaluate. A few studies found this thinning of inner layers to be diffuse or localized (superior, or both superior and inferior quadrants).3,4 While correlating the retinal nerve fiber layer (RNFL) with cognitive impairment, Kromer et al.5 showed that the global thinning of RNFL had fairly low MMSE (mini-mental state examination (MMSE) or Folstein test) scores ranging from 11 to 19 and from 8 to 28. An MMSE score greater than 27 out of 30 suggests normal cognition. However, Berisha et al. reported MMSE scores between 17 and 30 in subjects with RNFL thinning only in the superior sector. Furthermore, the superior sector could be used to discriminate between mild cognitive impairment and severe Alzheimer’s Disease,5 while there was no significant difference found between the RNFL thickness of mild cognitive impairment and mild Alzheimer’s Disease patients.

Histologic studies showed a 52% decrease in neuronal density in Alzheimer’s Disease.6 Bayhan et al. reported thinning of the ganglion cell thickness in individuals with Alzheimer’s Disease leading to thinning of the macular thickness with no significant change in outer retinal thickness.7 In this study, the scan was performed primarily on the temporal part of the fovea to achieve more information about the temporal area, which is the most commonly involved area in Alzheimer’s Disease. They also found a significant correlation between the macular ganglion cell thickness and MMSE scores. In regards to retinal function, Berisha et al. showed a correlation between the RNFL thickness and a number of pattern-electroretinogram characteristics, especially with the P50-N95 amplitude, but not with visual-evoked potentials.8

Marziani et al. used two instruments (RT-Vue® and Spectralis®) to evaluate RNFL in Alzheimer’s Disease. RT-Vue® measures RNFL and ganglion cell layer (GCL) together and the Spectralis® permits the quantification of the RNFL separately.9 They reported a reduction in only the inner layers (RNFL and RNFL and GCL combined) in Alzheimer’s Disease. However, they were unable to determine which layer—RNFL or GCL—was most affected in Alzheimer’s Disease.

Larrosa et al. evaluated the diagnostic ability of standard OCT parameters using linear discriminant function (LDFs) and logistic regression statistical analysis to detect the presence of Alzheimer’s Disease.10

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TABLE 1. Optical coherence tomography findings in neurological diseases.
The LDFs had two parts: retinal LDF were obtained using information from the nine early treatment diabetic retinopathy study (ETDRS) area thicknesses. Peripapillary LDFs were obtained using 768 points in a peripapillary scan (grouped to obtain 24 uniformly divided locations). They reported that the retina LDFs had only moderate diagnostic accuracy, while the RNFL LDFs were a very useful and precise tool for diagnosis of Alzheimer’s Disease. The LDFs were sensitive and specific as the methods currently used for Alzheimer’s Disease diagnosis.

**Multiple Sclerosis**

Multiple sclerosis presents commonly as optic neuritis characterized by recent vision loss associated with visual field loss, color desaturation, and pain with eye movement. Most of the patients recover to normal visual acuity levels; however, the quality of the vision is affected.

Inner retinal layers have been evaluated extensively using OCT in multiple sclerosis. Walter et al. reported that multiple sclerosis eyes had significant thinning of...
the inner retinal layers’ RNFL, GCL, and IPL (inner plexiform layer) compared with disease-free control eyes (Figure 1). They also found the degree of thinning is much greater in eyes with optic neuritis compared to non-optic neuritis eyes. Additionally, they reported that the retinal GCL, IPL, and RNFL thinning in multiple sclerosis patients was strongly correlated with visual function, quality of life, and disability tests such as high-contrast visual acuity (VA), low-contrast letter acuity (LCLA), National Eye Institute Visual Function Questionnaire (NEI-VFQ 25), and 10-Item Neuro-Ophthalmic Supplement composite score. Similarly, previous studies have shown significant peripapillary RNFL dropout in multiple sclerosis non-optic neuritis eyes.

Furthermore, non-optic neuritis eyes showed significant thinning of the macular RNFL with no difference in GCL, IPL, and other retinal layers when compared to controls. This could be due to subclinical episodes of optic neuritis or due to axonal loss with relative sparing of the retinal GCL. They suggested that GCL and IPL thickness measurement act as a potential structural marker of patient-reported visual disability. The literature suggests that thinning of GCL on OCT is similar to gray matter atrophy on magnetic resonance imaging (MRI) as the ganglion cells in the retina are analogous to gray matter in the brain.

Burgansky-Eliash et al. reported a LDF using combinations of RNFL parameters obtained from Stratus OCT to evaluate the detection of perimetric glaucoma. Similarly, Garcia-Martin et al. formulated LDF using peripapillary RNFL thickness parameters obtained from a Spectralis® OCT system for the detection of multiple sclerosis. They reported that the formulated LDF has the highest sensitivity (83.02%) at specificity compared to single RNFL parameters in detection of multiple sclerosis compared to controls. A likelihood ratio of higher than 3.14 for the LDF (cutoff point for 95% specificity) virtually rules out the chance of a patient having multiple sclerosis.

An additional tool was proposed by the same group using artificial neural networks (ANN) for RNFL parameters obtained by OCT. ANN are machine-learning algorithms that perform nonlinear classifications based on the representative and adequately large training data set. This approach produces robust classifiers which are insensitive to noise and outliers in the data. They reported a combination of these RNFL thickness measurements from 24 locations in the peripapillary area. The ANN technique offers better ability to detect RNFL damage than any single RNFL parameter. These techniques including LDF and ANN in combination with the other parameters and clinical explorations could be helpful with an early diagnosis or a nondefinitive multiple sclerosis diagnosis; however, further evaluation is warranted.

Overall, measurement of GCL and RNFL thicknesses by OCT may be a better way than brain MRI to detect and monitor axonal loss in multiple sclerosis due to its easier acquisition, better resolution, and better correlation with visual functions.

### OTHER DEMYELINATING DISEASE

#### Neuromyelitis Optica

Neuromyelitis optica (NMO), also known as Devic’s Disease, is a severe idiopathic inflammatory demyelinating disease characterized clinically by bilateral blindness, paraplegia or quadriplegia due to outbreaks of acute transverse myelitis associated with optic neuritis. The neuronal loss is more severe in NMO compared to multiple sclerosis. Studies report that
a single episode of NMO with optic neuritis leads to thinner RNFL compared to multiple sclerosis patients with at least a difference of 20 microns. This thinning is correlated with neurologic disability measured by the Expanded Disability Status Scale (EDSS) in NMO.

Non-multiple sclerosis patients with a history of unilateral optic neuritis longer than three months and with inter-eye RNFL thickness differences of 15 μm or more should be investigated for a NMO spectrum disorder.

**Longitudinally Extensive Transverse Myelitis**

Longitudinally extensive transverse myelitis (LETM) is characterized by acute transverse myelitis (ATM) involving more than three vertebral segments. It has a similar presentation to NMO-related myelitis with no evidence of optic neuritis but poorer prognosis and a higher risk of relapse.

Maura et al. evaluated LETM patients without any history of optic neuritis using OCT to evaluate subclinical optic nerve involvement. They found that the RNFL thickness in the nasal quadrant significantly reduced in LETM eyes and advised that subclinical focal damage is possible in LETM. In contrast, Ratchford et al. and de Seze et al. did not find any significant changes in RNFL thickness in eyes with non-optic neuritis in patients with LETM. Ratchford et al. suggested that the NMO rarely converts to a secondary progressive course, while multiple...
sclerosis leads to subclinical axonal damage either from recurrent attacks of inflammation or from slowly progressive axonal degeneration.  

### Parkinson’s Disease

Parkinson’s Disease (PD) is a degenerative disorder of the central nervous system, secondary to death of pigmented dopamine neurons in the substantia nigra of the midbrain, caused by the accumulation of the protein alpha-synuclein in neuronal Lewy bodies.  

Parkinson’s Disease is also associated with loss of other dopaminergic neurons such as retinal amacrine cells, leading to thinning of retinal ganglion cells.

Using time domain OCT, La Morgia et al. reported significantly thinner temporal RNFL in patients with PD compared to controls. Using spectral domain (SD)-OCT, Aaker et al. reported significant thinning in macular thickness. However, there was no significant reduction in peripapillary RNFL and inner retinal layer thickness between PD patients and controls. In contrast, Garcia-Martin et al. showed a reduction in both macular and RNFL measurements.

Garcia-Martin et al. used the “Nsite Axonal Analytics” application of Heidelberg to detect changes due to PD. As reported previously in Alzheimer’s Disease and multiple sclerosis, they formulated retinal LDF, which had sensitivity of 89.5%. They reported that the likelihood ratio value of 4.59 for retinal LDF rules out the chances of having PD. They recommended SD-OCT as a reliable diagnostic tool for subclinical PD diagnosis.

### Schizophrenia

Schizophrenia is a chronic, progressive neurocognitive disorder characterized by reduction in total brain volume. Defects in visual perception and processing in schizophrenia have been proposed to be secondary to dopamine dysregulation and excess of glutamate. Since the retina is an extension of the brain, it may lack myelination; thus, nerve fiber layer thinning represents axonal damage.

Lee et al. studied the structural OCT parameters, especially RNFL changes in schizophrenia patients in comparison to age-matched controls. They looked at patients with variable duration of illness and found that chronic (2 to 10 years) and long-term chronic (>10 years) schizophrenic patients have a significant peripapillary RNFL thinning, macular thinning, and reduction of macula volume when compared to controls ($P < 0.001$), and these features correlated with the duration of illness. They advised that OCT can play a major role in detecting worsening of neuronal degeneration by measuring the RNFL thickness.

Key findings in various neurological diseases are shown in Table 1.
AUTOIMMUNE RETINOPATHY

Autoimmune retinopathy presents with acute or chronic vision loss, nyctalopia, and photopsias. Findings include optic nerve pallor, retinal pigment epithelial (RPE) changes, vitreous cell and, most commonly, vascular attenuation with abnormal electroretinograms. Cancer-associated retinopathy (CAR), melanoma-associated retinopathy, and non-paraneoplastic associated retinopathy are included in this entity.

Abazari et al. reported focal loss of RNFL, disruption of the photoreceptor inner and outer segment (IS/OS) junction, and reduced retinal thickness in patients with newly diagnosed autoimmune retinopathy. Similar findings were reported by Mohamed and Harper in a patient with CAR secondary to endometrial adenocarcinoma and by Pepple et al. in patients with small-cell bronchogenic carcinoma, metastatic melanoma, breast, acute myelogenous leukemia, and cervical neuroendocrine cancers. Additionally, the latter correlated with loss of outer retinal layers on OCT with hyper-autofluorescence.

These OCT findings may help to perform the diagnosis of autoimmune retinopathy in unclear situations and to evaluate response to therapy.

HEMATOLOGICAL DISEASES

Sickle Cell Retinopathy

Sickle cell hemoglobinopathy is due to an inherited abnormal globin protein chain, which leads to intravascular sickling. Sickle cell retinopathy (SCR) could range from nonproliferative to proliferative forms. Histopathologic studies of SCR have shown selective atrophy of the inner retinal layers after macular infarction. Hoang et al. reported macular thinning with asymptomatic sickle cell disease (Figure 1). Central and parafoveal macular areas and outer retinal layers were significantly thin in these patients with no change in the inner retinal layers as compared to controls (Figure 2). They have suggested that the macular thinning could be from subclinical macular infarctions and outer retinal damage could be due to occlusion of choriocapillaris. Chow et al. correlated retinal function with macular thinning in sickle cell disease patients. The overall mean microperimetry retinal sensitivities was significantly less in eyes with macular thinning compared to patients without macular thinning. However, there was no statistical difference between patients without macular thinning. The degree of thinning correlated with the severity of temporal macular thinning. These patients may require different peripapillary RNFL thickness thresholds for future glaucoma evaluations.

In summary, outer retinal thinning may be a marker that would prompt more aggressive systemic management of sickle cell disease. The presence of macular thinning may serve as a screening tool to identify patients who would benefit from examination of the retinal periphery, either clinically or with wide-field FA.

Beta-Thalassemia

Beta-thalassemia is one of the abnormal inherited hemoglobinopathies. Eleftheriadou et al. reported small, round, hyperpigmented lesions bilaterally on clinical examination in patients with thalassemia, which were seen as granuloid-like accumulations at the RPE. Fluorescein angiography showed granular hyperfluorescence and hypofluorescence due to pigment decompensation. They suggested that these

FIGURE 3. Macular thickness maps of a 17-year-old female with sickle cell disease genotype SS who developed arterial occlusion in the right eye (A). Optical coherence tomography scan shows inner retinal hypere reflectivity with edema. Left eye (B) appears normal.
deposits could be due to occlusion of choriocapillaries which clinically represent as black sunburst lesions and resorbed salmon patch hemorrhages.

**Leukemia**

Ortiz et al. reported diagnosis of leukemia through ocular findings. They reported a case of serous detachment on OCT, leading to exudative retinal detachment during follow-up and eventually to a diagnosis of lymphoblastic acute leukemia. Another patient presented with sub-ILM (inner limiting membrane) hemorrhage with no other significant finding; this patient was evaluated further and diagnosed with chronic lymphoid leukemia.

Figure 4 shows a representative case of chronic myeloid leukemia which presented to us with sub-ILM hemorrhage.

**Human Immunodeficiency Virus (HIV) Infection**

HIV subjects have abnormal visual symptoms without any retinopathy, such as reduced sensitivity in the field of vision using both standard and short-wavelength perimetry, color and contrast sensitivity tests of central vision, and abnormality on electrophysiological tests. Pepose et al. reported loss of inner retinal structures, including the vasculature and ganglion cells, due to microangiopathy in HIV-positive patients.

Kozak et al. divided HIV subjects into three groups. Group A included HIV-negative patients with no history of ocular disease, who served as normal control subjects. Group B included HIV-positive patients who were never recorded to have CD4 cell counts below 100 cells/µL, had no significant ocular disease or eye surgery, and served as positive control subjects. Group C included HIV-positive patients with CD4 cell counts below 100 cells/µL at some point in their medical history lasting for at least six months. A statistically significant difference was observed in mean RNFL thickness between groups A and C ($P < 0.001$) and between groups B and C ($P < 0.001$) but no difference between groups A and B ($P < 0.05$). Group C differed from groups A and B in temporal, superior, and inferior sectors, respectively ($P < .05$, $P < .01$, and $P < .001$). No statistically significant difference in the nasal area was found among the groups. The authors concluded that significant RNFL thinning occurs in HIV patients without CMV retinitis and with low CD4 counts and that third-generation OCT may be useful in diagnosis of early subclinical HIV-associated visual functional loss. Arantes et al. correlated RNFL thinning in HIV-infected patients with low CD4 count with functional loss detected by a frequency doubling technology (FDT) perimeter.

In another study, Arantes et al. evaluated the spatial association between visual field (VF) sensitivity loss and RNFL thinning in patients infected by HIV. They found the strongest correlations between the superior RNFL measurements and inferior visual field zones and between the nasal RNFL measurements and temporal visual field zones.

In summary, RNFL thinning occurs before the development of clinically obvious HIV-related changes in the posterior segment of the eye, which correlates well with visual function.

**Migraine**

A migraine may present as visual, sensory, and motor phenomena. Tan et al. reported no reduction in RNFL thickness in migraine patients with or without aura compared to healthy individuals. Martinez et al. reported no difference in mean RNFL thickness between patients with migraine and healthy controls, except in the temporal quadrant. Gippono et al. found no difference in the foveal thickness and macular volume in females with migraine compared to healthy women, but found that there was a significant

![FIGURE 4. Fundus photograph of a 40-year-old male with acute myeloid leukemia showing sub-internal limiting membrane (ILM) haem at subfoveal location along with white-centered hemorrhage. Spectral domain optical coherence tomography scan shows hyperreflective lesion with shadowing confirms the sub-ILM location of hemorrhage.](image)
thinning in the RNFL thickness in the upper quadrant. Recently, Ekinci et al. reported significant thinning in RNFL and GCL in patients with migraine with aura in comparison to migraine patients without aura and the healthy controls.74

IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri (PTC), is a clinical entity that presents with elevated intracranial pressure (ICP), usually seen in obese women of child-bearing age, along with signs and symptoms of headaches, pulsatile tinnitus, visual changes, and papilledema.75 Papilledema associated with subsequent visual field loss is a dreaded consequence and this clinical presentation determines the management and outcome of IIH.76 However, clinical evaluation of the disc and subjective evaluation using a Frisen scale to evaluate longitudinal changes may be challenging.77

The Frisen scale is a non-continuous ordinal grading based on specific features described in fundus photographs or on ophthalmoscopy to assess and monitor the disc changes in papilledema.78 However, this scale reportedly lacks sensitivity to small changes in the degree of disc edema and the interpretation varies among observers.79,80 OCT, on the other hand, quantitatively assesses the multiple layers of the retina, allowing objective measurement of the RNFL thickness, and thereby helps with evaluation of longitudinal changes. Additionally, OCT offers several advantages over conventional photographic imaging, such as the ability to image eyes with small pupils and cataracts.81 Patients with newly diagnosed IIH show RNFL thickening when compared to healthy controls (Figure 5). This RNFL thickness decreased over time with treatment of IIH (Figure 6). Therefore, RNFL thickness could be a potential longitudinal measure in the management of IIH.76,81 Wang et al. developed an automated method for the quantification of volumetric optic disc swelling on SD-OCT imaging in individuals with papilledema.82 They further investigated for correlation of volumetric measurements with Frisen scale grades (from fundus photographs) and two-dimensional RNFL and total retinal thickness measurements from SD-OCT. Their results suggested that volumetric measurements of the degree of disc swelling in individuals with papilledema appeared to be roughly linearly correlated to the Frisen scale grade.83 Other reports have also concurred that, in newly diagnosed IIH, OCT demonstrated alterations of the peripapillary retina and optic nerve head (ONH) correlate with the Frisen grading scale, but not with clinical features or visual dysfunction.84

Increased peripapillary retinal thickness measured by OCT is associated with increased ICP in newly diagnosed IIH patients.85 However, in long-standing IIH patients who have been previously treated, OCT appears to be of limited value in predicting ICP. Similarly, Rebolleda and Muñoz-Negrete reported that RNFL thickness abnormalities assessed by OCT in patients with mild papilledema were quantitatively correlated with visual field sensitivity losses as determined by automated perimetry. However, the drawback with OCT is that, when the thickness is decreasing, it is not possible to distinguish whether it is the effect of treatment or there is actual loss of nerve fibers.86 In such a setting, GCL analysis may provide more accurate information than RNFL analysis, and it might be an early structural indicator of irreversible neuronal loss.87 One must always rule out other possible causes of vision loss, such as submacular fluid, choroidal folds, or any other concurrent maculopathy.

To overcome the previously discussed drawbacks, Kaufhold et al. proposed a new, custom segmentation algorithm using an extension of the RPE through the ONH as a reference line, which enabled them to automatically assess ONH volume and shape in IIH patients that could be applicable in diseases with elevated ICP and optic disc swelling.76 Their pilot study found that their proposed 3D parameters—Optic Nerve Head Volume (ONHV) and Optic Nerve Head Height (ONHH)—were able to discriminate between controls and treated and untreated patients. Both ONHV and ONHH measures were related to levels of intracranial pressure (ICP).76 Hence, SD-OCT can be used as a tool to differentiate between papilledema and pseudopapilledema; further strengthening the view, it can be used in the assessment and monitoring of the optic disc in IIH.87

Another current advance in OCT technology is phase contrast OCT, which allows visualization of the capillaries and quantification of blood flow within the capillary bed without the use of contrast agents.77

In summary, there is growing evidence that suggests the use of OCT as a noninvasive quantitative method of monitoring the amount and evolution of papilledema as disc volume that correlates with RNFL and peripapillary total retinal thickness.76,77 Therefore, OCT may obviate the need for repeated lumbar punctures to measure the opening pressure to assess papilledema progression. At present, the most beneficial OCT-derived features pertinent to papilledema are measurement of disc volume, thickness of retinal GCL, and appearance of subretinal
fluid. Furthermore, OCT can help differentiate causes of visual loss in IIH and predict the outcome.\textsuperscript{76,77,86}

**CHOROIDAL METASTASIS**

Choroidal metastasis is the most common intraocular malignancy in adults. Reports have shown that 8% of patients who died of malignancy showed choroidal metastases on autopsy.\textsuperscript{88} Anatomically, because the choroid is rich in vasculature, it acts as a most common site for metastasis within and around the eye.\textsuperscript{89} Uveal metastases outnumber orbital metastases by a ratio of 8 to 1.\textsuperscript{89,90}

Newer developments in imaging have led to better understanding of choroidal metastasis. While fundus auto-fluorescence best defines surface characteristics and tumor margins, OCT better demonstrates intraretinal findings such as atrophy, subretinal fluid, and loss of RPE.\textsuperscript{91}

OCT features of choroidal metastasis arising from the breast and lung were initially reported by Arevalo et al.\textsuperscript{92} The findings include anterior displacement of the photoreceptor layer by subretinal fluid accumulation, loss of normal retinal architecture due to subretinal deposits, and Juliano et al. described comparable results in a case of bilateral choroidal metastases, along with areas of hyper-intense irregularities in the photoreceptor layer (Figure 7).\textsuperscript{93}
OCT was reported to be a useful tool for follow-up of choroidal metastasis after treatment by Pérez-Alvarez, but limited to superficial choroidal location of the metastasis. This limitation—i.e., inadequate imaging of the choroid—can be circumvented using Enhanced Depth Imaging (EDI) SD OCT. Torres et al. reported that EDI SD-OCT allows better visualization of the choroidal metastasis with low reflective band in the deeper choroid and enlargement of the suprachoroidal space. The other advantage of the system is the ability to concurrently show the choroidal tumor and associated retinal changes. It was reported that the inner limit of the sclera is identifiable on the image, which permits accurate measurement of tumor thickness. Al-Dahmash et al. later used EDI-OCT on 14 eyes with choroidal metastases to assess the deeper retinal and choroidal

FIGURE 6. Fundus photographs of a 32-year-old lady with chronic Idiopathic Intracranial Hypertension (IIH) on treatment; the right eye (A) shows disc edema and the left eye (B) shows edema and onset of pallor. The corresponding OCT images (C) show retinal nerve fiber layer thinning in both eyes (left more than right).
morphology, and found a characteristic “lumpy bumpy” choroidal surface along with compression of the overlying choriocapillaris and irregularities of the outer retinal layer. The characteristic appearance of tumors on EDI SD-OCT helps with identifying other intraocular tumors, such as melanoma and choroidal lymphoma.

Demirci et al. observed EDI-OCT features of choroidal metastasis with plateau surface, shaggy photoreceptors, and subretinal fluid with speckles. It has been reported that EDI-OCT can also identify subclinical choroidal metastases barely seen with indirect ophthalmoscopy. Furthermore, EDI-OCT allows detection of micro-metastases often not seen during fundoscopy.

To summarize, EDI OCT helps to diagnose and follow-up choroidal metastases which are clinically and ultrasonographically too subtle to appreciate.

**OPTIC NERVE DISEASE**

OCT has provided better understanding of the effect of optic nerve pathology, not only in terms of the effect on the optic nerve itself, but also in terms of the associated retinal and macular findings, which may contribute to vision loss in optic nerve diseases.

### Papilledema

The swelling of the optic nerve tissue in papilledema may be associated with the presence of fluid in the surrounding tissues, including the peripapillary zone and the macula. In eyes with papilledema, subretinal fluid in the peripapillary region is a common finding, which contributes to enlargement of the blind spot, peripapillary hyperopia, and refractive scotomas.

Patients with papilledema and reduced visual acuity may have macular edema, which can be demonstrated on OCT, as shown by Hoye et al. in 2001. They studied 19 patients with acute, subacute, or recurrent papilledema who underwent macular OCT. Seven patients were found to have subretinal fluid involving the macula and all seven had a reduction in visual acuity. The visual acuity in these patients improved with resolution of the macular subretinal fluid.

Savini et al. described a hyporeflective subretinal space on macular OCT in eyes with papilledema. They hypothesized that extensive swelling of the optic nerve head may anteriorly displace the peripapillary nerve fiber layer, producing a tractional separation between the sensory retina and the RPE. This hyporeflective subretinal space seen on OCT in papilledema may actually be an artifact secondary to a thickened and more reflective RNFL and may not represent true fluid. Figure 8 shows a case of papilledema with RNFL thickening in both eyes.

### Vitreopapillary Traction

Traction on the optic disc by the adjacent adherent vitreous body may result in an elevation of the ONH with blurring of the disc margins and a subretinal hyporeflective space. Hedges et al. have described two cases of pseudo papilledema in which OCT imaging demonstrated vitreopapillary traction and the disc appearance returned to normal after vitrectomy in one case.

### Diabetic Papillopathy and Papillitis

Diabetic papillopathy with minimal or no diabetic retinopathy may result in sub-macular fluid accumulation. Fluorescein angiography in such cases proved that the fluid is a result of leakage from the ONH rather than a disruption of the blood retinal barrier. Diabetes-mellitus-induced glial dysfunction may accelerate transretinal fluid movement in such cases.

### Ischemic Optic Neuropathy

Non-arteritic ischemic optic neuropathy (NAION) may also be associated with the presence of peripapillary and/or subretinal fluid, as described by...
Hedges et al. This subretinal fluid may contribute to some of the visual loss associated with NAION and the visual acuity reduction roughly correlated with the degree of increased macular thickness. Consequently, partial visual recovery may be a result of the resolution of the sub-macular fluid. Figure 9 shows a case of NAION with RNFL thickening (Figure 8).

**Microcystic Retinal Changes**

Spectral domain OCT imaging has demonstrated microcystic changes in the inner nuclear layer in certain patients with optic atrophy. Such changes have been described in patients with neuromyelitis optica-related optic neuritis. Recent studies have shown the presence of similar microcystic changes in the...
inner nuclear layer also in cases of Leber’s hereditary optic atrophy, dominant optic atrophy, compressive optic neuropathy, glaucomatous optic atrophy, and hydrocephalus.\textsuperscript{106-111} Damage or destruction of the axons forming a part of the optic nerve may ultimately result in trans-synaptic degeneration, which may manifest as microcystic changes in the inner layers of the retina where the bodies of these cells may lie. This theory is supported by findings of experiments conducted in primates by Van Buren in 1963 which showed the presence of cavitory degeneration in the inner nuclear layer after optic nerve crush injury.\textsuperscript{112}

**Optic Pathway Gliomas**

Optic pathway glioma (OPG) presents with visual impairment in children with neurofibromatosis(NF)-1. This clinical feature is used as a threshold to start chemotherapy and follow-up in these children. Parrozzani et al. studied 57 patients with NF-1 with recent orbital/brain MRI showing OPG and reported RNFL thinning with statistically significant sensitivity and positive predictive value for detecting the lesion.\textsuperscript{113,114} Avery et al. studied 89 eyes with OPG and found that thinning of the RNFL had a statistically significant association with reduction of visual acuity.\textsuperscript{115} Gu et al. have reported that thickness of macular GCL-IPL and macular RNFL are significantly reduced in children with OPG-related vision loss compared to those with normal vision.\textsuperscript{116} Numerically, 88.9% of those with decreased GCL-IPL thickness had vision loss. Thus, the macular GCL-IPL thinning can be considered as a strong predictor of visual impairment in these patients and an indication to start chemotherapy.

These children often have a coexistent impairment of cognitive function, which makes it difficult to assess the visual acuity in them. SD-OCT plays an important role in such a scenario by detecting thinning of the RNFL as an early sign of optic atrophy consequent of OPG.

**Astrocytic Hamartomas**

SD-OCT can be used to detect occult retinal astrocytomas that may be clinically not possible to detect on ophthalmoscopy or color fundus photography. Xu et al. used infrared imaging and SD-OCT to document occult retinal astrocytomas in two of four patients in a single center study in patients with tuberous sclerosis.\textsuperscript{117} The lesions were found to be originating from the RNFL with overlying vitreous adhesions, showing hyperreflective dots and optically empty spaces at all depths of the tumor.

Shields et al. also described the SD-OCT imaging of retinal astrocytomas in 15 consecutive eyes of 14 patients as showing hyperreflectivity at the surface, internal retinal disorganization, and a gradual gently sloping transition from a normal retina into a tumorous retina in all 15 cases (100%).\textsuperscript{118} Other features included were retinal traction on the surface of the tumor, discrete internal moth-eaten optically empty spaces representing intrallesional calcification or intratumoral cavities, and optical shadowing posterior to the tumor owing to intrallesional calcification or cavities (Figure 10). Some lesions also showed shallow elevation of the adjacent retina, adjoining retinal edema, and macular edema.

In conclusion, OCT imaging has contributed to a better understanding of primary optic nerve pathology and the associated macular and retinal structural changes, which contribute to vision loss.

**RENAL DISEASES**

Ocular findings in Alport Syndrome include anterior lenticonus and dot-and-fleck retinopathy with an associated dull macular reflex or “lozenge” sign,\textsuperscript{119} along with systemic involvement of the kidney and ear.\textsuperscript{120} Ahmad et al. reported temporal retinal thinning on OCT in patients with Alport Syndrome, but weak correlation of temporal macular thinning with visual function tests such as microperimetry and multifocal electroretinography.\textsuperscript{121} Hence, it was suggested that the macular thickness measurements are essential in the diagnosis and prognosis of Alport Syndrome.

In patients on hemodialysis, Yang et al. reported no significant change in macular volume and RNFL, but choroidal thickness was reduced after hemodialysis.\textsuperscript{122} This could be due to an autoregulatory mechanism.

**WHIPLASH INJURY**

Whiplash maculopathy is rare.\textsuperscript{123} Mavrakanas et al. reported a perifoveal lesion on clinical examination which showed an abnormal vitreo-retinal interface on OCT.\textsuperscript{124} The lesion was correlated with sensitivity loss, measured by quantified perimetry, suggesting an underlying retinal damage. These changes could be due to vitreoretinal traction. Recent results of macular histological examination following a fatal whiplash injury support the pathogenic role of vitreoretinal traction in photoreceptor disruption.\textsuperscript{125}

**SHAKEN BABY SYNDROME**

Ocular findings in Shaken Baby Syndrome include pre-retinal, intra-retinal, or sub-retinal hemorrhages, vitreous hemorrhage, and macular retinoschisis with blood in between the layers.\textsuperscript{126,127} Using time-domain OCT, Sturm et al. reported vitreoretinal traction and
Recently, Scott et al. demonstrated retinoschisis with blood in between the layers using hand-held OCT. The extension of such sub-ILM hemorrhage up to the optic nerve has also been reported.

**DRUG TOXICITY**

**Deferoxamine Retinopathy**

Deferoxamine is an iron-chelating agent used to treat chronic iron overload in patients with hematologic conditions requiring routine blood transfusion. Animal experiments and histology studies in human eyes with deferoxamine retinopathy have shown that the degenerative process affects primarily the RPE and Bruch’s membrane.

Viola et al. reported various RPE degenerative presentations in the macula on clinical examination, which were similar to pattern dystrophies. The most common presentation was the presence of small, yellow-gray lesions, seen on OCT as focal thickenings or bumps of the RPE, resembling basal laminar drusen. The second common presentation was radiating yellow pigment lines associated with granular and focal areas of brown hyper-pigmented material, resembling a butterfly-shaped dystrophy. There areas corresponded to thickening of the IS/OS junction and thinning of the RPE on SD-OCT. The third type of

![Optical coherence tomography scan of a 12-year-old male with astrocytic hamartoma, showing disorganization of retinal architecture with optically empty cavities within the tumor mass.](image)
presentation was yellowish subretinal flecks resembling fundus flavimaculatus. The flecks corresponded to granular hyper-reflective subretinal deposits on SD-OCT scans, extending into the outer plexiform layer (OPL) and interrupting the overlying external limiting membrane (ELM). On follow-up, SD-OCT revealed progressive interruption of the outer retinal layers and RPE atrophy and marked thinning of the outer nuclear layer (ONL). The fourth type was a rounded, yellowish sub-macular lesion in each eye, resembling a vitelliform dystrophy, seen in OCT as homogeneous hyperreflective material in the subretinal space above the RPE, associated with a diffusely thickened IS/OS junction but intact ELM. On follow-up, there was progressive resolution of the hyper-reflective subretinal material, until RPE atrophy occurred at two years, with loss of the macular IS/OS junctions, absence of the ELM, and marked thinning of the ONL (Table 3).

Wu et al. reported the SD-OCT features of multiple confluent hyper-reflective deposits in the choroid, RPE and IS/OS junction, Bruch’s membrane, and choroid space, in a 34-year-old male with deferoxamine retinopathy. These effects were seen extending from the perifovea to the peripheral retina with foveolar sparing.\(^{133}\)

**Sildenafil**

Sildenafil citrate, a cyclic guanosine monophosphate-specific phosphodiesterase-5 (PDE-5) inhibitor, has a vasodilatory effect and is used commonly in erectile dysfunction and pulmonary hypertension. Vasodilatation leads to an increase in choroidal blood flow, which could either affect RPE function (predisposing the patient to serous retinal detachment) or conversely be useful in the treatment of ocular diseases to increase the choroidal blood flow.

Kim et al. evaluated seven healthy males to demonstrate anatomic and physiologic changes in the choroid following systemic sildenafil citrate using EDI-OCT and swept-scan high-frequency digital ultrasound. Two hours following sildenafil administration, an average increase of 11.6% temporal to the fovea, 9.3% nasal to the fovea, and 10.7% underneath the fovea (\(p < 0.001\) for all values) was observed in all eyes.\(^{134}\) Vance et al.\(^{135}\) reported an increase in mean choroidal thickness by 12.3% at one hour and 11.6% at three hours after ingestion of sildenafil.

**Tamoxifen**

Tamoxifen is used as an adjuvant endocrine therapy for women with hormone-responsive breast cancer. Ocular manifestations of tamoxifen include tamoxifen retinopathy, vortex keratopathy, induction of posterior subcapsular cataract, and optic neuritis. Tamoxifen retinopathy is caused by oxidative damage due to its cationic amphiphilic properties.\(^{136}\)

Georgalas et al. reported bilateral extensive areas of disruption in inner retinal layers in a patient with no signs of crystalline retinopathy after 10 years of tamoxifen therapy.\(^{137}\) Doshi et al. reported pseudocystic foveal cavitation similar in appearance to macular telangiectasia type 2 on SD-OCT, probably due to toxicity to retinal Muller cells.\(^{138}\) Similar findings have been seen in previous reports.\(^{139}\) Patients receiving tamoxifen should be monitored with high-resolution OCT for fundoscopically invisible changes in the inner retinal layers, the progression of which may seriously affect the patient’s vision and subsequently their quality of life.

**Hydroxychloroquine and Chloroquine**

Retinal toxicity is the major and most serious irreversible side-effect of hydroxychloroquine.\(^{140}\) Risk of toxicity increases to 1% after using it for five to seven years or cumulative dose accumulation of 1000 g of hydroxychloroquine.\(^{141}\)

**FIGURE 11.** Fundus photograph (top image) of a 50-year-old male on hydroxychloroquine therapy showing retinal pigment epithelial (RPE) atrophy (arrow), which is seen as hypoauflorescence (arrow, middle image) on an auto fluorescence image. Spectral domain optical coherence tomography scan shows outer retinal damage with RPE atrophy (arrow, bottom image).
Ulviye et al. compared SD-OCT findings in patients who had systemic lupus erythematosus disease and were under treatment with hydroxychloroquine for less than five years with healthy controls and found that there was perifoveal thinning in the superior, nasal, and inferior quadrants in these patients. Korah et al. also reported similar loss of ganglion cell layers, causing marked thinning of the parafoveal region in a patient with rheumatoid arthritis who was on chloroquine for the past three years. Stepien et al. reported loss of IS/OS junction and a downward “sinkhole” displacement of inner retinal structures in areas of hydroxychloroquine toxicity corresponding to HVF 10-2 defects and ophthalmoscopic clinical examination findings (Figure 11).

FIGURE 12. Fundus photographs of a 48-year-old lady with vision loss due to toxic optic neuropathy due to ethambutol. The disc photograph of the right eye (A) shows hyperemia of the optic disc and the left eye (B) shows retinal nerve fiber hemorrhage. The corresponding optical coherence tomography image (C) showing minimal thinning of the retinal nerve fiber layer in the right eye.
Ethambutol

Ethambutol-induced optic neuropathy has a predilection for the papillo-macular bundle of the RNFL, making the ONH changes often subtle and easy to miss on funduscopic examination (Figure 12). Zoumalan et al. reported a mean thinning of 72% RNFL in the temporal quadrant, with an average mean optic nerve thickness of 26 ± 16 µm in patients with ethambutol-induced optic neuropathy. There was a combined mean loss of 46% of fibers from the superior, inferior, and nasal quadrants in the (six) eyes of all three subjects (mean average thickness of 55 ± 29µm).

Lead

Ekinci et al. evaluated the toxic effects of chronic lead exposure on retinal RNFL thickness, macular thickness, and choroidal thickness in battery industry workers and reported significant ocular changes due to chronic exposure. Hence, these parameters should be evaluated during ophthalmologic examination of individuals working in lead-based industries.

In conclusion, OCT findings are useful to predict the probability of a disease, to diagnose it early, to differentiate between healthy and unhealthy tissue, and to assess the effect of therapeutic interventions in many systemic diseases. However, it is difficult to extrapolate the absolute quantitative data directly into routine clinical practice. This review summarizes the retinal findings on OCT and explores their application in systemic conditions.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES


