Neurological Diseases

1

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Abstract

Imaging has become an integral part of the management of retinal diseases. Being window to the brain, imaging of the posterior segment is useful in evaluating neurological diseases. These imaging findings are used for early diagnosis to correlate with severity of the disease and to monitor progression. This chapter describes important findings on imaging modalities in neurological disease and their clinical implications.

1.1 Introduction

The eyes are the windows to the brain. Various neurological diseases affect eyes, and in many of them, they provide the first clue to the systemic disease. In many, other than clinical follow-up, there is no marker for severity of the disease.

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

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and choroid. There are multiple reports on OCT findings in these neurological diseases ranging from the commonly occurring diseases like Parkinson's disease and Alzheimer's disease to the rarer disorders like schizophrenia. OCT findings have been reported to be beneficial in early diagnosis of neurological diseases as well as to understand and follow the course of these diseases.

This chapter summarizes the important and useful OCT findings of the retina reported in various neurological diseases and their clinical applications.

1.1.1 Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia among the numerous causes, and its incidence increases exponentially with age. AD is primarily a disease of the brain. Besides cognitive abnormalities, various visual function impairments are noted including color perception, depth perception, contrast sensitivity, and visual field measures, these being the common complaints which have shown to decrease the quality of life of the patients even at the early stage of the disease [1]. Earlier these were believed to be due to the malfunction of the central visual pathways [2, 3]; however, Hinton et al. [4] showed that these changes could be due to the axonal degeneration of optic nerves in patients with AD.

It is a well-known fact that the retina is an extension of the brain, derived from the neural tube like other structures of the brain [5], and various studies have shown the eye especially the retina to be involved in AD [4, 6, 7].

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 retinal ganglion layer, as the retina and brain share similar responses to inflammation [8]. Such stress situations are particularly relevant to the exposed and metabolically sensitive retinal ganglion cells (RGC) and photoreceptor cells. Interestingly, in 2008, both the retinal and choroidal vascular Aβ deposits were reported in animal models of AD [9]. This lead to the use of optical coherence tomography to study these changes in the retina in patients with AD.

Iseri et al. demonstrated a relation between reduction in macular volume and the severity of cognitive impairment using time-domain OCT [7]. Due to limitations of the device, changes in the individual layer were not possible to be evaluated. Few studies found this thinning of inner layers as diffuse or localized (superior or both superior and inferior quadrants) [10, 11]. While correlating thinning of the retinal nerve fiber layer (RNFL) with cognitive impairment, Kromer et al. [12] 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. 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 [12], while there was no significant difference found between the RNFL thickness of mild cognitive impairment and mild Alzheimer's disease patients.

Histologic studies showed 52% decrease in neuronal density in Alzheimer's disease [13]. 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 [14]. In this study, the scan was performed primarily on the temporal part of the fovea to achieve more information, 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 regard 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 [15].

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 [16]. They reported reduction in only the inner layers (RNFL and RNFL and GCL combined) in Alzheimer's disease. However, they were unable to determine which layer either RNFL or GCL was most affected in Alzheimer's disease.

Larrosa et al. evaluated diagnostic ability of standard OCT parameters using linear discriminant functions (LDFs), and logistic regression statistical analysis, to detect the presence of Alzheimer's disease [17]. 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 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.

To sum up, many studies have reported a significant decrease in the mean overall RNFL thickness in patients with AD, and some have reported significant reductions in the individual quadrants. The superior and inferior quadrants demonstrating the greatest thinning in patients with AD compared with healthy controls in most studies, whereas the nasal and temporal quadrants are only found to be significantly thinner in few studies [18].

A meta-analysis done in 2015, based on 11 studies, suggested that AD patients are likely to have a reduced RNFL thickness as assessed by OCT. This reduction in RNFL thickness, as observed in most studies on AD patients, was significantly greater than that observed in the age-matched controls and thus cannot be exclusively ascribed to aging [19]. Further, the analysis showed a uniform significant decrease in RNFL thickness in each of the four retinal quadrants, suggesting that whatever factors that cause the degenerative process in AD progression affects the entire retinal layer.

Thus to conclude, the OCT technique for measurement of the peripapillary RNFL and macular thickness is useful for the potential correlation with the severity of the disease which in turn could help in early diagnosis of the disease.

1.1.2 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 [20]. Parkinson's disease is also associated with loss of dopaminergic neurons such as retinal amacrine cells leading to thinning of retinal ganglion cells. It also leads to loss of similar neurons in the higher visual areas (e.g., lateral geniculate nucleus, cholinergic nucleus basalis of Meynert, and visual cortex) [21]. Levodopa, a dopamine precursor, is released by human retinal pigment epithelial (RPE) cells [22, 23]. Looking at it differently, the dopamine loss in patients with PD may be in part because of the thinning of the RPE [24].

Motor-related problems are the usual features seen in the early disease and cognitive and behavioral ailments occurring in the late stages. Affected foveal vision with decreased contrast sensitivity and color vision and altered visual-evoked potentials in patients with PD have been described previously. These have been attributed to the dysfunction of the intraretinal dopaminergic circuitry and final retinal output to the brain [25, 26].

These changes in the retinal layers are thought to be of help in early diagnosing of a case of PD. Multiple studies have reported RNFL changes in PD [24, 27–29].

Using time-domain OCT, La Morgia et al. reported significantly thinner temporal RNFL in patients with PD compared to controls [30]. Using spectral domain (SD)-OCT, Aaker et al. reported significant thinning in macular thickness [31]. 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 [32].

Garcia-Martin et al. used "Nsite Axonal Analytics" application of Heidelberg to detect changes due to PD [33]. 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.

In conclusion, PD is still a commonly encountered disease among aging population, but the accuracy of the clinical diagnosis of PD is still limited. Especially in the early stages, when cardinal symptoms are not conclusive, diagnosis can be delayed as structural neuroimaging methods such as CCT or MRI do not provide characteristic features that allow the diagnosis of this chronic neurodegenerative disorder [34]. Apart from the early diagnosis of PD, serial RNFL recordings can be done to monitor the progression of the disease as well. Recently in a meta-analysis of 13 case-control studies done by Ji-guo Yu et al. in 2016, it was concluded that the RNFL thickness decreased in all quadrants in PD patients compared with the healthy control group and that the OCT can be useful in monitoring the disease progression [35].

1.1.3 Migraine

Migraine is a widely encountered condition in the general population. According to data from the American Migraine Prevalence and Prevention study, the cumulative lifetime incidence of migraine was reported to be 43% in women and 18% in men [36].

Ophthalmologists are often the first to evaluate the patients with migraine due to the accompanying ocular complaints like periorbital pain, photophobia, and other visual disturbances.

Although there are a considerable number of studies and theories on the pathophysiology of migraine, the exact nature of the condition is still considered to be unknown [37]. Currently, migraine is accepted as a neurovascular syndrome resulting from the activation of the nociceptors that innervate the meningeal blood vessels.

Recent reports have demonstrated direct electrophysiological evidence for the activation of trigeminovascular neurons during a migraine attack. The dura mater is largely innervated by the sensory nerve fibers originating from the trigeminal ganglion. Sensorial innervation of the eye is also supplied by the trigeminal nerve. Long and short ciliary nerves, which originate from the ophthalmic division of the trigeminal nerve, innervate various structures in the eye. Short ciliary nerves also carry autonomic nerve fibers, which innervate the choroidal vasculature [38, 39].

Tan et al. reported no reduction in RNFL thickness in migraine patients with or without aura compared to healthy individuals [40]. Martinez et al. reported no difference in mean RNFL thickness between patients with migraine and healthy controls except in the temporal quadrant [41]. 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 thinning in the RNFL thickness in the upper quadrant [42]. 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 [43].

In another recent study, Zeynep Dadaci et al. found that in patients with unilateral headaches, the choroidal thickness measurements obtained during the attack period were significantly increased only in the eyes on the headache side compared to basal levels. At the fovea, the choroidal thickness measured in the pain-free interval was 373.45 ± 76.47 μm (mean ± SD), which increased to 408.80 ± 77.70 μm during the attack period ($p < 0.001$).

The findings obtained from the various abovementioned studies can be valuable in understanding the pathophysiology of migraine and its association with normal tension glaucoma, better keeping in mind the common innervation of the meninges and the eye by the trigeminal nerve.

1.1.4 Schizophrenia

Schizophrenia is among the top ten leading causes of disease-related disability in the world because of the pervasiveness of associated deficits and frequently lifelong course.

It is a chronic and relapsing illness with generally incomplete remissions. It is characterized by an admixture of positive, negative, cognitive and mood symptoms [44]. Schizophrenia has been associated with deficits in visual perception and processing [45, 46]. Dopamine is established to be a major neurotransmitter and

modulator in the retina by Djamgoz et al. [47] and may be responsible for these visual changes in neurodegenerative diseases. But unlike Parkinson's disease wherein dopamine levels are reduced, in schizophrenia these levels are raised. Possibly excess glutamate leading to neural excitotoxicity could be contributory to the neurodegenerative process of schizophrenia [48]. Glutamate has been shown to act as a neurotoxin, which exerts its toxic effect causing destruction of retinal ganglion cells [49]. Retina lacks myelin; hence, any changes in retina reflect axonal damage following any brain tissue damage [44].

Putting all this together, structural changes in the retina specifically RNFL changes are expected in these patients. Only few studies have been done in schizophrenic patients to evaluate the RNFL changes so far.

The first study done in 2010 by Francisco J. et al. reported that schizophrenic patients showed a statistically significant reduction of the overall RNFL thickness (95 ± 13 μm) compared with those values observed in control eyes (103 ± 8 μm) and also observed reduced peripapillary RNFL thickness in nasal quadrant (75 ± 17 μm) when compared with controls (84 ± 10 μm). The remaining peripapillary RNFL quadrants, macular thickness, and volume did not reveal differences between both groups.

Another study by Chu EM et al. performed OCT in 38 schizophrenia, 11 schizoaffective disorder, and 40 matched healthy controls and found out that patients and controls had similar whole retina RNFL thickness ($p = 0.86$) and macular volume (MV) ($p = 0.64$), but RNFL in the right nasal quadrant of the schizoaffective group was thinner than in the schizophrenia group ($p = 0.02$).

Lee et al. studied the structural OCT parameters especially RNFL changes in schizophrenia patients in comparison to age-matched controls [44]. They looked at patients with variable duration of illness and found that chronic (2–10 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.

In conclusion, OCT can have a major role in detecting worsening of neuronal degeneration by measuring the RNFL thickness especially when used in correlation with MRI since the latter is an established method to know the progression of the disease by measuring the volumetric brain volume reduction. With more researches in the future, it is hoped that OCT can be a useful investigative tool in schizophrenia and can be used to monitor the progression of disease.

1.1.5 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. They also found the degree of thinning is much greater in eyes with optic neuritis compared to non-optic neuritis eyes [50] (Fig. 1). Additionally, they reported that the retinal GCL, IPL, and RNFL thinning in multiple sclerosis patients was strongly correlated with visual function, quality of

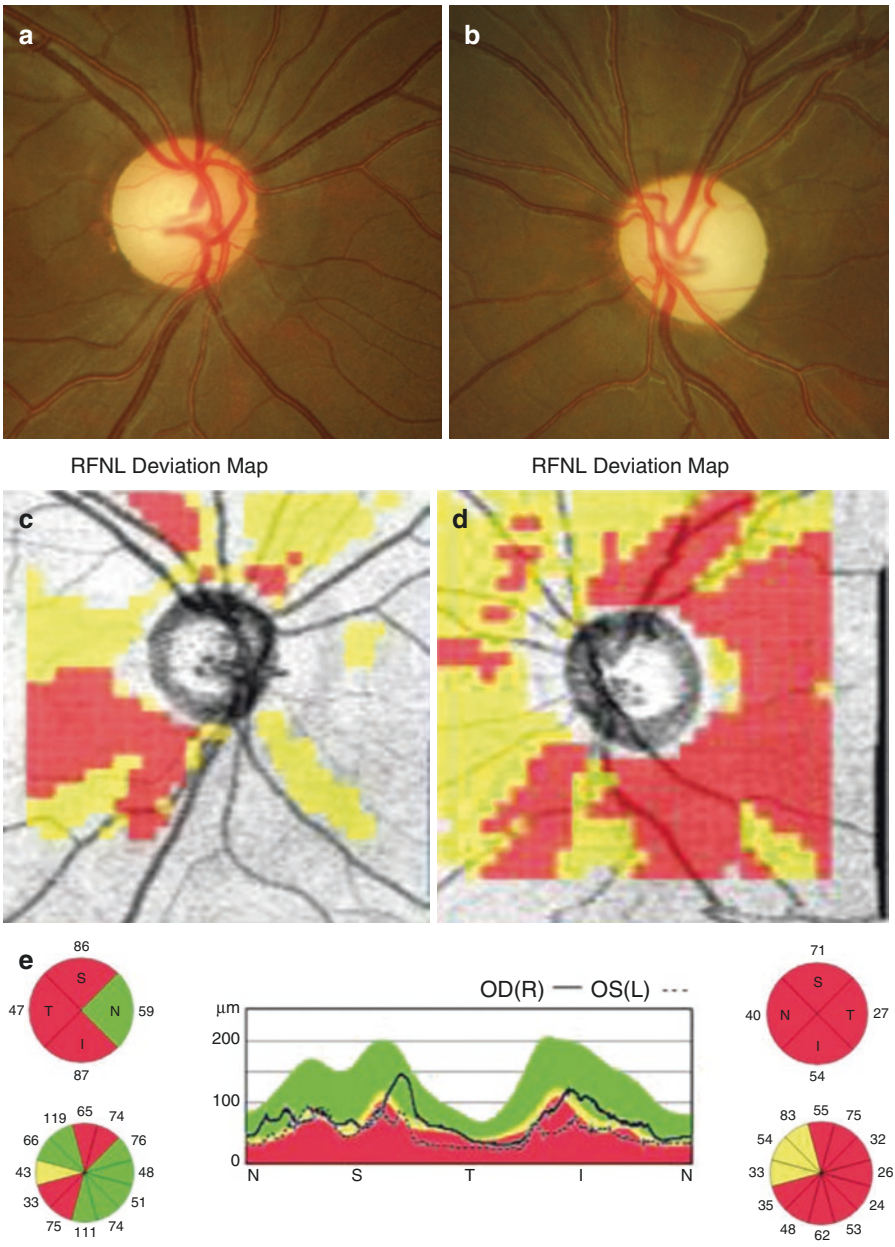

Fig. 1.1 Optic disc photographs of an 44 year old lady with multiple sclerosis, showing pallor of both optic nerves (**a**, **b**). OCT scans show advanced changes on the RNFL deviation maps (**c**, **d**) and severe RNFL thinning (**e**, **f**)

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 ten-item Neuro-Ophthalmic Supplement composite score [50]. Similarly, previous studies have shown significant peripapillary RNFL dropout in multiple sclerosis non-optic neuritis eyes [51–53].

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 [54, 55]. 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 [56, 57].

Burgansky-Eliash et al. reported a LDF using combinations of RNFL parameters obtained from Stratus OCT to evaluate the detection of perimetric glaucoma [58]. Similarly, Garcia-Martin et al. formulated LDF using peripapillary RNFL thickness parameters obtained from Spectralis® OCT system for the detection of multiple sclerosis [59]. They reported that the formulated LDF has the highest sensitivity (83.02%) and specificity compared to single RNFL parameter 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 patient having multiple sclerosis.

Another 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 [60]. They reported a combination of these RNFL thickness measurements from 24 locations in the peripapillary area. 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 no definitive 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 [60].

1.2 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 [61]. Papilledema

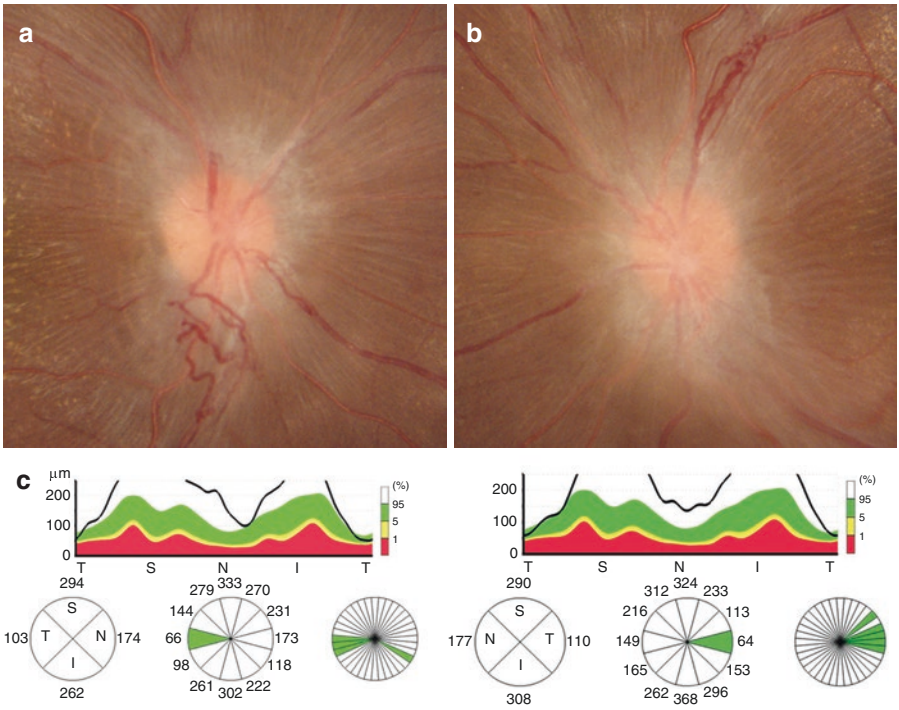

Fig. 1.2 Optic disc photo graphs showing disc edema (**a**, **b**) with blurring of the peripapillary retinal nerve fibre layer (RNFL), in a 19 year old lady, diagnosed with IIH with normal vision and color vision . The corresponding RNFL OCT (**c**) scan shows increased RNFL thickness

associated with subsequent visual field loss is a dreaded consequence, and this clinical presentation determines the management and outcome of IIH [62]. However, clinical evaluation of the disk and subjective evaluation using Frisen scale to evaluate longitudinal changes may be challenging [63].

The Frisen scale is a noncontinuous ordinal grading based on specific features described in fundus photographs or on ophthalmoscopy to assess and monitor the disk changes in papilledema [64]. However, this scale reportedly lacked sensitivity to small changes in the degree of disk edema and the interpretation varies among observers [65, 66]. 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 (Figs. 2 and 3). Additionally, OCT offers several advantages over conventional photographic imaging such as ability to image eyes with small pupils and cataracts [66]. Patients with newly diagnosed IIH show RNFL thickening when compared to healthy controls. This RNFL thickness decreased over time with treatment of IIH. Therefore, RNFL thickness could be a potential longitudinal measure in the management of IIH [62, 67]. Wang et al. developed an automated method for the quantification of volumetric optic disk swelling on SD-OCT imaging in individuals with papilledema [68]. They further

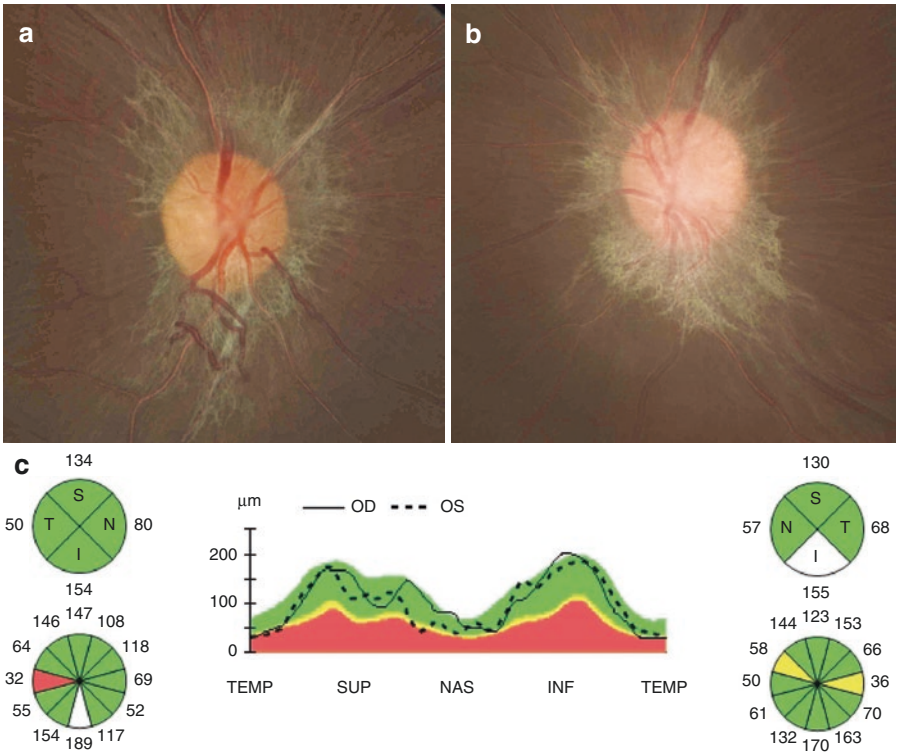

Fig. 1.3 Optic disc photo graphs (**a**, **b**) of the same patient showing a reduction disc edema with peripapillary gliosis, after 4 months of oral acetazolamide therapy. OCT (**c**) of the same patient shows a significant decrease in the RNFL thickness as compared to the earlier scan (Fig. 1) and is now within the normal range

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 disk swelling in individuals with papilledema appeared to be roughly linearly correlated to the Frisen scale grade [69]. Other reports have also concurred that in newly diagnosed IIH, OCT demonstrated alterations of the peripapillary retina and optic nerve head (ONH) correlate with Frisen grading scale, but not with clinical features or visual dysfunction [70].

Increased peripapillary retinal thickness measured by OCT is associated with increased ICP in newly diagnosed IIH patients [69]. 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 [71]. 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 [72]. 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 above-discussed drawbacks, Kaufhold et al. proposed a new custom segmentation algorithm using an extension of the RPE through the ONH as 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 disk swelling [62]. 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, treated and untreated patients. Both ONHV and ONHH measures were related to levels of intracranial pressure (ICP) [62]. 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 disk in IIH [73].

Another current advance in OCT technology is phase contrast OCT, which allows visualization of capillaries and quantification of blood flow within the capillary bed without the use of contrast agents [63].

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 disk volume that correlates with RNFL and peripapillary total retinal thickness [62, 63]. 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 disk 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 [62, 63, 72].

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