Original Article

Optical coherence tomography in papilledema and pseudopapilledema with and without optic nerve head drusen

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Aim: To compare the spectral domain optical coherence tomography (SD-OCT) findings of the optic disc and the peripapillary retina of patients with a true papilledema and pseudopapilledema with and without optic nerve head drusen (ONHD). **Study Design:** Retrospective Case Control Study. **Subjects and Methods:** Peripapillary retinal nerve fiber layer (PPRNFL) thickness as depicted by SD-OCT of 94 eyes of 66 patients with papilledema (30 eyes), pseudopapiledema (31 eyes), and normal controls (33 eyes) was analyzed. The mean RNFL thickness, total retinal thickness (TRT) at a superior and inferior edge of the disc and the quadrant wise topography of increased RNFL were compared in all three groups. Sensitivity, specificity, and area under the receiver operating characteristic curve (AROC) were calculated for all the parameters. **Results:** The median RNFL thickness was 185.4 (129.5–349.3 μm), 122.3 (109–156.3 μm) and 91.62 ± 7 μm in papilledema, pseudopapilledema, and controls, respectively. Papilledema group had thicker PPRNFL in all quadrants except temporal quadrant. TRT was thicker in papilledema and pseudopapilledema compared to controls. ONHD could be directly visualized as high reflective clumps in the sub-retinal space or the RNFL in 30 eyes. Increased RNFL thickness in all four quadrants was noted 43.3% in papilledema and 9.7% in pseudopapilledema. Normal RNFL thickness in all four quadrants was noted in 0% in papilledema and 32.3% in pseudopapilledema. Nasal RNFL had the highest AROC (0.792) indicating high diagnostic ability to differentiate papilledema from pseudopapilledema. **Conclusion:** SD-OCT can be used as a tool to differentiate between papilledema and pseudopapilledema.

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.149136

Quick Response Code:

Key words: Optic nerve head drusen, optical coherence tomography, papilledema, pseudopapilloedema

To diagnose and confirm pseudopapilledema in patients with buried optic nerve head drusen (ONHD) who are often misdiagnosed as idiopathic intracranial hypertension (IIH) often poses a diagnostic dilemma. Similarly, children presenting with a history of headaches with elevated discs and no visual complaints present a difficult situation for the treating ophthalmologist. In the above scenarios, a confirmatory test to document an ONHD can save the patient from undergoing unnecessary invasive investigations and prolonged unwarranted treatment. Ultrasound, fundus fluorescein angiography (FFA), and a computed tomography (CT) of the orbits have been used to diagnose the ONHD which is seen as a hyper-reflective echo on the ultrasound B scan and a hyper-dense lesion at the optic nerve head on the CT.[1,2] Autofluorescence has also been described to diagnose ONHD.[2] But in the absence of a documented ONHD by the above-mentioned investigations, it is very difficult to steer the course of further treatment in these patients. We prefer to term these patients as pseudopapilledema without evident ONHD (pseudopapilledema without disc drusens [PWD]). This category also includes anomalous discs classically described as small discs with no cup and anomalous branching of the blood vessels. The purpose of this study was to determine the findings on spectral domain optical coherence tomography (SD-OCT) in documented cases of true papilledema (TP), documented cases of ONHD (pseudopapilledema with disc drusen [PD]) and PWD.

Optical coherence tomography has been used in the literature to detect mild papilledema.[3] Peripapillary retinal nerve fiber layer (PPRNFL) thickness comparisons in patients with ONHD and optic disc edema, and normal controls have been performed with time domain (TD)-OCT and in spectral domain (SD-OCT).[4,5] Recently, the direct visualization of ONHD has been shown using the SD-OCT.[5]

Subjects and Methods

The OCT videos and images of 94 eyes of 66 patients who had presented to Medical Research Foundation, Chennai from September 2010 to May 2013 were assessed retrospectively. The criteria for selection were inclusion of all patients who had a swollen optic disc secondary to papilledema, clinically evident ONHD, buried ONHD and had undergone an OCT evaluation. All the patients included in the papilledema group had undergone magnetic resonance imaging (MRI) brain with magnetic resonance venography (MRV) and a lumbar puncture to document the cerebrospinal fluid opening pressure and bio-chemical analysis. Patients were divided into the clearly defined three groups. First group was papilledema, which was defined as bilateral disc edema secondary to a documented elevated intracranial pressure (ICP) (as checked with a manometer) with a normal MRI with MRV brain. The second group was pseudopapilledema, which was further divided into PWD and PD. All the patients with PD had ONHD documented on the ultrasound B scan or CT or FFA. PWD was defined as patients with optic disc swelling in the absence of symptoms of raised ICP and normal optic nerve function tests (visual

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Manuscript received: 21.08.14; Revision accepted: 23.11.14

acuity, pupils, color vision, and Humphrey visual fields) and a persistence of disc edema on future follow-up. Thirty eyes of 15 patients were included in the first group, 11 eyes of 7 patients in PD and 20 eyes of 11 patients in PWD. Thirty-three eyes of 33 patients were taken as normal control group which was taken as the third group.

All OCT scans were performed by single examiner (MKP). All the patients included in the study were tested using SD-OCT. Twenty-nine patients and 33 normals were imaged on Cirrus high definition (HD)-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) using optic disc scan 200 × 200 protocol and four patients were imaged on three-dimensional (3D)-OCT 1000 (Topcon, Inc., Tokyo, Japan) using RNFL circle scan and 3D scan 256 × 256. In Cirrus HD-OCT, the optic disc scan 200 × 200 is a 6 mm × 6 mm cube consisting of 200 B-scans with 200 A-scans per B-scan in which RNFL thickness is measured along the circle of radius 1.73 mm. In Topcon 3D-OCT 1000, RNFL thickness was taken from circle scan of diameter 3.4 mm centered at optic disc. 3D scan 256 × 256 was used for qualitative assessment of the optic disc, which consisted of 256 B-scans and 256 A-scans per B-scan in a 6 mm × 6 mm cube. All OCT were performed after pupillary dilatation. Scans with poor signal strength and artefacts were excluded. RNFL thickness in all four quadrants, average RNFL thickness, and total retinal thickness (TRT) were taken for analysis. TRT was measured manually from internal limiting membrane to the inner boundary of retinal pigment epithelium (RPE) using calipers at inferior and superior edges of the optic disc. Qualitative assessment of the disc and morphology of the disc swelling was performed. At final follow-up, all the patients with papilledema had resolution of disc edema after treatment. All 11 eyes with PD had calcification on ultrasound B-scan.

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, SPSS Inc, version 14). All parameters were checked for normality using Kolmogorov–Smirnov test. The OCT measurements were compared among TP (Group 1), pseudopapilledema (Group 2) with and without obvious ONHD and normal controls (Group 3). RNFL thickness in all quadrants and average RNFL thickness were compared using Kruskal–Wallis test followed by *post-hoc* Mann–Whitney test. Inferior and superior TRT were compared using one-way analysis of variance followed by *post-hoc* Bonferroni test. *Post-hoc* conservative *P* value was considered as < 0.016. Receiver operating characteristics (ROC) curves were used to find the diagnostic ability of OCT parameters in distinguishing papilledema and pseudopapilledema from controls and between papilledema and pseudopapilledema. ROC curve is plotted between sensitivity and 1 specificity. The area under curve (AUC) was used to quantify the distinguishing ability of the parameter. An AUC of one indicates a perfect discrimination while an AUC of 0.5 is chance discrimination. The level of significance was considered as <0.05.

Table 1: Demographic details of study patients

Parameters	Papilledema	Pseudopapilledema	Controls
Sample size	30	31	33
Age (years)*	33.6±8	28.8±10	33.2±11.3
Gender (Male:Female)	12:18	16:15	18:15

*Mean±SD. One-way ANOVA, *P*=0.478. SD: Standard deviation, ANOVA: Analysis of variance

Results

Table 1 shows demographic details of study participants. The mean age of patients in papilledema, pseudopapilledema, and normal groups was not statistically significant (*P* = 0.478).

Retinal nerve fiber layer thickness

Table 2 gives the RNFL thickness values in papilledema, pseudopapilledema, and controls. In papilledema, the RNFL thickness was maximum in the inferior quadrant and least in the temporal quadrant. In pseudopapilledema, it was maximum in the superior quadrant and least in the temporal quadrant, but logically in this group, it is based on the location and depth of drusen and can vary from case to case. Comparison of RNFL thickness between the three groups using Kruskal–Wallis test showed a statistical significant difference between the groups (*P* < 0.001) with RNFL being the thickest in all four quadrants in papilledema than other two groups. *Post-hoc* Mann–Whitney test with the conservative *P* value of 0.016 showed a statistical significant difference in RNFL thickness between the groups (*P* < 0.001) except temporal RNFL which showed no statistical significant difference between papilledema and pseudopapilledema (*P* = 0.066).

Peripapillary total retinal thickness

Table 2 gives the mean TRT at inferior and superior edge of the optic disc. The mean inferior and superior TRT was increased in papilledema than pseudopapilledema, but the difference was not statistically significant (*P* > 0.016, *post-hoc* Bonferroni test). The difference in the mean TRT between Groups 1 and 3 and also Groups 2 and 3 was statistically significant (*P* < 0.001).

Table 2: Peripapillary RNFL thickness for all four quadrants, average RNFL thickness and TRT at inferior and superior edge of the optic disc in the three groups; papilledema, pseudopapilledema, and controls

Parameters (μm)	Papilledema (*n*=30)	Pseudopapilledema (*n*=31)	Controls (*n*=33)	*P*
Superior RNFL	225.5 (168.5-477.5)	167.2±52.6	124.88±12.37	<0.001
Inferior RNFL	264.5 (154.2-417.3)	153 (129-234)	126±11.78	<0.001
Temporal RNFL	89.5 (69.8-172.3)	75 (63-97)	64.97±5.2	<0.001
Nasal RNFL	161.5 (100.8-288)	100.55±37.49	75±7.5	<0.001
Average RNFL	185.4 (129.5-349.3)	122.3 (109-156.3)	91.62±7	<0.001
Inferior TRT	666±280.6	543.7±143.7	367.6±30	<0.001
Superior TRT	690.3±291.4	572.4±116.7	370.1±30.7	<0.001

RNFL: Retinal nerve fiber layer, TRT: Total retinal thickness

Topography of disc swelling on optical coherence tomography

In papilledema, the RNFL thickness was increased in all four quadrant in 43.3% (13 eyes), increased in three quadrants with normal thickness temporally in 30% (9 eyes), increased only nasally in 6.7% (2 eyes), increased only superiorly in 6.7% (2 eyes), increased only inferiorly in 6.7% (2 eyes), increased in three quadrants with normal thickness inferiorly in 6.7% (2 eyes). In pseudopapilledema, the RNFL thickness was normal in all four quadrants in 32.3% (10 eyes), increased inferiorly and nasally in 19.4% (6 eyes), increased superiorly and nasally in 12.9% (4 eyes), in all four quadrants in 9.7% (3 eyes), increased superiorly in 6.5% (2 eyes), increased in three quadrants with normal thickness temporally 6.5% (2 eyes), superiorly and inferiorly in 3.2% (1 eye), increased inferiorly in 3.2% (1 eye), all quadrants except nasally 3.2% (1 eye), all quadrants except inferiorly 3.2% (1 eye).

Optical coherence tomography in pseudopapilledema with evident optic nerve head drusen

All 11 eyes with PD had a high reflective echo above the RPE or in the RNFL [Figs. 1 and 2]. The RNFL thickness was normal in all four quadrants in 4 eyes (36.4%), increased in the superior quadrant in 2 eyes (18.2%) and inferiorly in 1 eye (9.1%), increased in all four quadrants in 2 eyes (18.2%) and inferiorly and nasally in 2 eyes (18.2%).

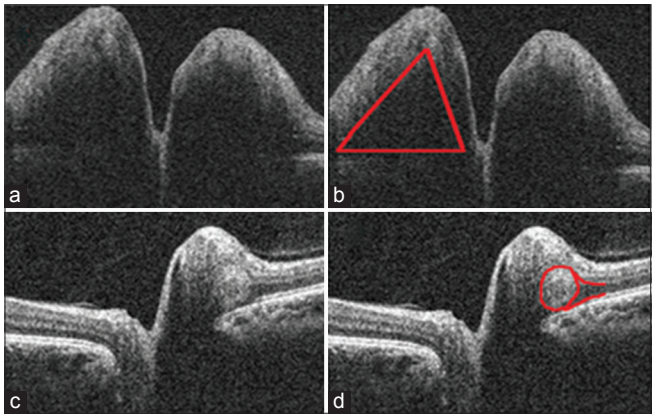

Figure 1: The triangular subretinal hyporeflective space in papilledema (a, b) and the buried optic nerve head drusen in pseudopapilledema (c, d)

Optical coherence tomography in pseudopapilledema without evident optic nerve head drusen

Nineteen of 20 eyes with PWD revealed a hyper-reflective echo above the RPE in the peripapillary retina especially in the nasal retina [Fig. 1]. In 1 eye with PWD, the disc edema was secondary to the vitreo-papillary traction. In PWD, the RNFL thickness was normal in 6 eyes (30%), increased inferiorly and nasally in 4 eyes (20%), increased superiorly and nasally in 3 eyes (15%), increased in all except temporally in 2 eyes (10%), increased all except inferiorly 1 eye (5%), all except nasally 1 eye (5%), increased superiorly and inferiorly 1 eye (5%), increased in all quadrants except nasally 1 eye (5%), increased in all quadrants in 1 eye (5%).

Optical coherence tomography in papilledema

All 30 patients with TP had OCT taken during the acute phase of raised ICP. All patients with papilledema had a resolution of disc edema after the treatment. The RNFL thickness decreased after the commencement of treatment [Fig. 3].

Ability of optical coherence tomography parameters to differentiate between 3 groups

Table 3 gives the AUC, the cut-off point, sensitivity, and specificity of the OCT parameters in differentiating Group 1 and 2 from controls (Group 3) and papilledema from pseudopapilledema. Average RNFL had the highest AUC followed by nasal, superior and inferior RNFL indicating its highest diagnostic ability in differentiating papilledema from controls. Inferior TRT had the highest AUC indicating its diagnostic ability in differentiating between pseudopapilledema and controls. In distinguishing papilledema from pseudopapilledema, nasal RNFL had the highest AUC with a cut-off point of 113.5 microns resulting in a sensitivity and specificity of 73% and 71%, respectively. TRT and temporal RNFL had a lesser AUC, which was not statistically significant ($P > 0.05$).

Discussion

This study reiterates the role of OCT in detecting disc edema and also in differentiating a TP from pseudopapilledema to some extent. A literature review on the use of OCT in papilledema and pseudopapilledema can be summarized as follows.

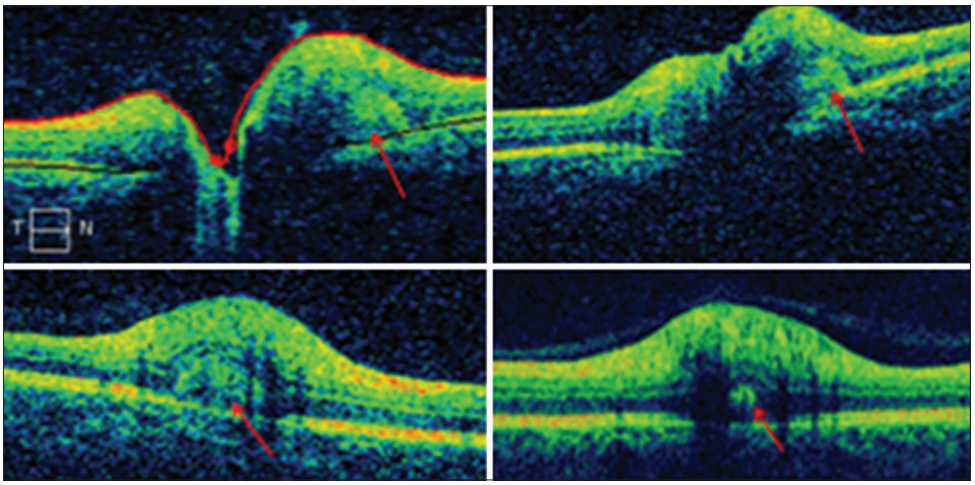

Figure 2: Buried optic nerve head drusen seen as a round hyperreflective echo (red arrow) above the retinal pigment epithelium

Table 3: AROC for OCT parameters to detect papilledema, pseudopapilledema and to differentiate between the two

Parameters (μm)	Cut-off point (μm)	AUC (95% CI)	Sensitivity %	Specificity %	*P*
Papilledema versus controls					
Average RNFL	103.8	1 (0-1)	100	100	<0.001
Superior RNFL	139	0.943 (0.871-1)	90	88	<0.001
Inferior RNFL	138.5	0.943 (0.887-0.997)	87	82	<0.001
Temporal RNFL	68.5	0.847 (0.737-0.958)	83	82	<0.001
Nasal RNFL	89.5	0.968 (0-1)	90	100	<0.001
Inferior TRT	399.5	0.892 (0.806-0.977)	80	82	<0.001
Superior TRT	390.5	0.871 (0.772-0.97)	83	70	<0.001
Pseudopapilledema versus controls					
Average RNFL	104.6	0.715 (0.57-0.86)	81	100	0.003
Superior RNFL	135.5	0.775 (0.648-0.901)	71	82	<0.001
Inferior RNFL	132.5	0.771 (0.647-0.896)	71	70	<0.001
Temporal RNFL	68.5	0.745 (0.609-0.881)	74	82	0.001
Nasal RNFL	76	0.715 (0.57-0.86)	74	61	0.003
Inferior TRT	399	0.858 (0.742-0.972)	83	82	<0.001
Superior TRT	402.5	0.98 (0-1)	97	82	<0.001
Papilledema versus pseudopapilledema					
Average RNFL	133.3	0.778 (0.664-0.893)	70	65	<0.001
Superior RNFL	170.5	0.762 (0.643-0.882)	77	65	<0.001
Inferior RNFL	172.5	0.726 (0.6-0.851)	70	61	0.002
Temporal RNFL	77.5	0.637 (0.497-0.777)	63	55	0.066
Nasal RNFL	113.5	0.792 (0.68-0.904)	73	71	<0.001
Inferior TRT	526.5	0.6 (0.453-0.747)	63	48	0.187
Superior TRT	544.5	0.582 (0.428-0.737)	63	52	0.278

TRT: Total retinal thickness, RNFL: Retinal nerve fiber layer, AROC: Area under the receiver operating characteristic curve, AUC: Area under curve, CI: Confidence interval, OCT: Optical coherence tomography

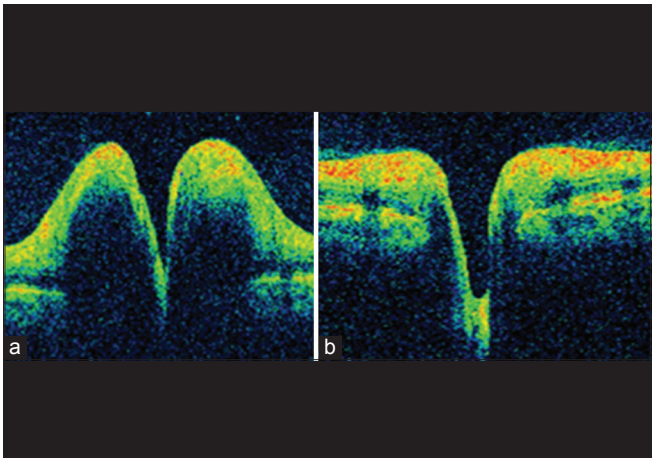

Figure 3: Pre- (a) and post-treatment (b) retinal nerve fiber layer in papilledema

Use of optical coherence tomography in diagnosing papilledema

In 2001, Hoye *et al*. studied the macular and optic disc OCT of 55 patients with papilledema and demonstrated separation of the retina from the underlying choroid by sub-retinal fluid in association with decreased visual acuity in seven cases.[6] They also proposed a direct communication between the sub-retinal space in the macular region and the swollen optic nerve. Though a later study by Waisbourd *et al*. stated that the fast macular thickness map did not demonstrate a significant difference between papilledema group and the normals for most measured macular areas. Savini *et al*. studied the stratus OCT findings in optic disc edema due to various pathologies including the papilledema and identified a hyporeflective subretinal space (possibly representing subretinal fluid) above the RPE.[7,8] Meridian scans of the optic nerve disclosed this space as having a triangular shape. The widest part of the triangle abutted the side of the optic nerve head; the tapered apex pointed away. The origin of this space was explained by the hypothesis is that extensive swelling of the optic nerve head pushes the nerve fibers overlying the disc anteriorly, and as these fibers are attached to the RNFL over the retina. We have also noted the presence of a triangular hypo-reflective space above the RPE in disc swelling due to papilledema. The significantly thickened RNFL causes intense shadowing behind which appears as a hyporeflective space [Fig. 1]. Scott *et al*. compared the stratus OCT and color fundus photographs and Modified Frisén scale (MFS) of the discs in papilledema and noted that the effect of papilledema can be seen on RNFL thickness and on RNFL TRT.[9] A disproportional increase of TRT above that of the RNFL represents fluid from neurosensory retinal detachment in the peripapillary retina. Therefore, OCT TRT may show proportionally more change per degree of disc edema than OCT RNFL thickness. They showed a stronger correlation of MFS grade with TRT compared with RNFL thickness suggests that more emphasis should be placed on

total retinal measurements. Similar results were published by Skau *et al*. again favoring TRT as a more reliable parameter compared to RNFL thickness as an indicator of papilledema.[10] Recent studies have evaluated the disc swelling using HD-OCT. Vartin *et al*. used SD-OCT to study the OCT findings in 24 eyes with papilledema.[3] They reiterated the usefulness of TRT in the detection of the early papilledema stating that the TRT measurement increases the sensitivity of detection of mild papilledema compared with conventional RNFL measurement. Kupersmith *et al*. examined the biomechanical deformation of load-bearing structures of the ONH resulting from raised ICP, using HD-OCT.[11] Papilledema with IIH results in an inward bowing of the RPE Bruch's membrane (BM) layer at the NCO not typically seen in normal eyes or other forms of disc edema. Although the sclera is not imaged clearly or completely by HD-OCT, the angulation and displacement of the RPE/BM presumably reflects deformation of the underlying peripapillary sclera and lamina cribosa in response to an elevated pressure gradient between the retrolaminar subarachnoid perioptic nerve sheath compartment and the globe.

Use of optical coherence tomography in monitoring papilledema

In pediatric patients with papilledema, an objective method of evaluation of disc swelling while monitoring the treatment is an easy option. El-Dairi *et al*. have shown the feasibility and accuracy of the same in pediatric age group.[12] Rebolleda and Muñoz-Negrete have quantitatively correlated RNFL thickness with visual field sensitivity losses.[13] They showed that for every 10 μm of mean RNFL thickness increase at baseline, there was a 0.6-dB decrease in mean deviation at the last follow-up. The main problem using OCT to observe patients with papilledema, is there is no way, based on OCT alone, to determine, when RNFL thickness returns toward normal, whether it implies patients are improving or that they are actually losing nerve fibers. A discrepancy between OCT and visual field testing can be helpful. Hence, serial OCT imaging and perimetry can be the standard in monitoring papilledema. Since all our patients showed a decrease in papilledema after initiation of treatment, the serial OCT showed a decrease in the RNFL thickness in all the patients [Fig. 3]. We also noticed discrete hyper reflective echoes above the RPE in patients with resolving papilledema at the level of the watermark sign seen in regressing disc swellings [Fig. 4]. OCT can definitely be used as a tool to monitor the treatment in IIH.

Use of optical coherence tomography in pseudopapilledema

Initial studies using the TD-OCT looked at the RNFL thickness in mild papilledema and pseudopapilledema and the results as to the difference between the thickness in both the groups were variable with Karam and Hedges reporting no statistically significant difference between the two groups and Johnson *et al*. stating that the differences in mean RNFL thickness between papilledema and ONHD were significant.[4,14] Johnson *et al*. also described a qualitative criteria for differentiating papilledema and pseudopapilledema using stratus OCT, he described the disc appearance on the OCT of papilledema as an elevated optic nerve head with smooth internal contour and subretinal hyporeflective space (SHYPS) with recumbent "lazy V" pattern whereas ONHD displayed a "lumpy-bumpy" internal optic nerve contour and a rapid decline in SHYPS thickness.[4] In our study also, the SHYPS was noted in papilledema (as mentioned previously) and in pseudopapilledema. Fig. 1 describes the difference between the shapes of this hyporeflective space in the two conditions: (a) The triangular space is larger in papilledema and appears smaller in pseudopapilledema, (b) the wider part of the triangle abuts the buried drusen which appears as a discrete hyperreflective echo just as described by Lee *et al*.[5] Another study by Wester *et al*. with stratus OCT studied the OCT differences between the ONHD, papilledema and small crowded discs.[15] They described ONHD as typically elevated disc surface on the OCT and appeared as an optically empty cavity, sometimes with a perceptible reflection from the posterior surface whereas in papilledema, there was strong anterior reflection due to which to structures were seen behind it. In congenitally crowded disc there is a minimal anterior reflection with slight elevation of the optic disc. More recent studies with SD-OCT have been able to look at the morphology

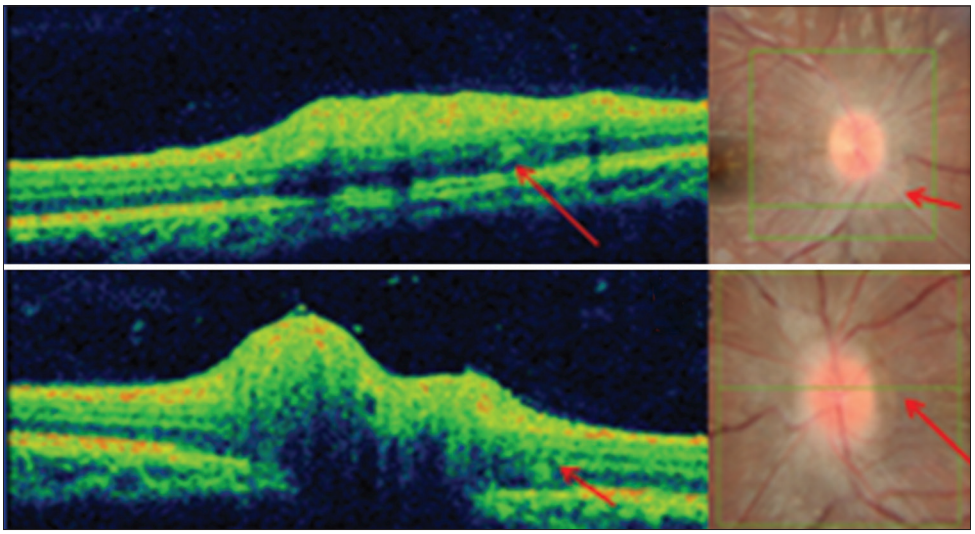

Figure 4: In resolving papilledema at the level of the watermark sign a discrete hyperreflective echo seen above the retinal pigment epithelium

of the ONHD and a congenitally anomalous disc in more detail. Lee *et al*. have described ONHD as a focal, hyperreflective, subretinal mass with a discrete margin on SD-OCT.[5] This study states that the retinal nerve fiber thickness in the nasal section provides a good differential marker for optic disc edema from ONHD. In our study of the 20 eyes of 11 patients with a doubtful diagnosis of pseudopapilledema, 19 eyes of 10 patients revealed a hyperreflective mass under the peripapillary retina especially in the nasal retina [Fig. 2] just as described by Lee *et al*.[5] In one patient, the pseudopapilledema was secondary to vitreopapillary traction which can be easily identified on the SD-OCT as described by Houle and Miller[16] Hence, in all (100%) patients with pseudopapilledema with a buried drusen, the ONHD was seen on OCT. Flores-Rodríguez *et al*. in their recent paper have suggested that there is no significant difference between TD-OCT and SD-OCT in diagnosing a pseudopapilledema and that the new quantitative parameters of papillary elevation and RNFL measurements showed greater sensitivity and specificity than the qualitative criteria which probably are seen better on the SD-OCT. Karam and Hedges argued that the study group in all the studies in favor of using OCT as a tool to differentiate between disc edema and pseudopapilledema had subjects with variable causes of disc swelling in the group with disc edema and could not be used to represent papilledema.[14,17] We found that in children, the ONHD is associated with normal RNFL thickness and as the age advances the RNFL thickness profile changes probably secondary to the progressive displacement of the fibers by the buried drusen.

Conclusion

Spectral domain optical coherence tomography can differentiate between papilledema, pseudopapilledema, and a normal disc. (a) If the RNFL thickness is normal in all four quadrants, it is more in favor of pseudopapilledema as none (0%) of the patients with TP had a normal RNFL thickness in all four quadrants. Similarly, increased RNFL thickness in all four quadrants is more suggestive of papilledema. (b) The direct visualization of the ONHD is the most important feature on SD-OCT to differentiate between pseudopapilledema and papilledema as the ONHD could be visualized on OCT in all (100%) eyes with buried drusen. (c) Nasal RNFL thickness has the highest diagnostic ability to differentiate TP from pseudopapilledema.

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Cite this article as: Bassi ST, Mohana KP. Optical coherence tomography in papilledema and pseudopapilledema with and without optic nerve head drusen. Indian J Ophthalmol 2014;62:1146-51.

Source of Support: Nil. **Conflict of Interest:** None declared.