Detection of mild papilloedema using spectral domain optical coherence tomography

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ABSTRACT
Objective To propose a method of diagnosis of mild papilloedema (PO) using peripapillary total retinal (PTR) thickness measurement by spectral domain optical coherence tomography (OCT).

Methods 24 eyes in 24 patients with PO caused by increased intracranial pressure and 22 eyes in 22 normal subjects were studied. OCT high-quality fundus images were analysed and graded by three masked observers using the Modified Frisén Scale. Eyes with PO were divided into two subgroups: those with mild PO (n=18) and those with moderate-severe PO (n=6). Two methods of measurements were evaluated and compared: retinal nerve fibre layer (RNFL) thickness measurements using standard optic disc cube 200×200 acquisition protocol and PTR thickness measurements using the ‘macular’ cube 512×128 acquisition protocol centred on the optic disc. Thickness values were calculated globally and for each quadrant (temporal, superior, nasal, inferior) and compared among the three groups (control, mild PO, moderate-severe PO). The main outcome measures were RNFL and PTR thickness.

Results Average RNFL and PTR thickness in the moderate-severe PO, mild PO and control groups were 299.3±10.9, 112.4±6.3, 96±5.7 and 804.5±17, 463.1±9.8 and 332.4±8.9 μm, respectively. Moderate-severe PO differed from mild PO and control groups using both RNFL thicknesses and PTR thicknesses measurements. Mild PO did not differ from controls using RNFL thickness measurement (p=0.17), but was statistically different using PTR thickness measurement (p<0.001).

Conclusion PTR thickness measurement increases the sensitivity of detection of mild PO compared with conventional RNFL measurement. This new way of using OCT may be useful for clinicians to detect mild PO.

INTRODUCTION
Papilloedema (PO) is an optic disc swelling secondary to axoplasmic flow stasis in the optic nerve head that results from raised intracranial pressure (ICP). Until a few years ago, diagnosis of PO relied solely on fundus examination and retinal angiography. Optical coherence tomography (OCT) may help in this diagnosis by showing peripapillary retinal nerve fibre layer (RNFL) thickening. Fixed standard 3.4 mm-diameter circular scans centred on the optic nerve head are commonly used to measure the peripapillary RNFL thickness. Measurement of RNFL thickness is a sensitive and specific discriminator of atrophic diseases of the optic nerve.1–3 Measurement of RNFL thickness has also demonstrated its usefulness in the diagnosis of optic disc swelling.4–7 However, OCT RNFL thickness measurements may miss mild PO.5–7 Previous work in severe PO demonstrated the existence of a hypo-reflective space above the retinal pigment epithelium (RPE), which may represent subretinal fluid accumulation in the peripapillary region.4–6 8–10 We investigated the hypothesis that the measurement of the total retinal thickness, between the internal limiting membrane and the RPE, would be a more sensitive method to discriminate PO than the measurement of the RNFL thickness, which is limited to the internal retinal layers. In order to measure the peripapillary total retinal thickness (PTR), we adapted new three-dimensional imaging protocols of spectral domain OCT. To the best of our knowledge, this is the first comparative study of RNFL and PTR thickness in PO and normal optic disc using spectral domain OCT.

METHODS
Population
The patient population comprised 24 patients (six men and 18 women) (mean age 30 years, range 11–65 years) having raised ICP at some point in their clinical course. The aetiologies of PO included idiopathic intracranial hypertension (16 patients), expansive lesions (five patients), subarachnoid haemorrhage (one patient), hydrocephalus (one patient) and cerebral venous sinus thrombosis (one patient). The mean duration of the clinical course of the patients with mild PO and moderate-severe PO were 255 (range 5–1181) days and 111 (range 10–387) days, respectively.

The control group comprised 22 normal subjects (mean age 39 (range 16–58) years) without neurological disease.

Exclusion criteria for both patients and normal subjects were: eyes with high ametropia (refractive error more than 5 D equivalent sphere or 3 D of astigmatism refraction), ocular disease (cataract, choriotoretinitis scars, posterior uveitis, macular degeneration or oedema, retinal artery or vein obstruction, laser therapy), the presence of any optic disc changes (glaucoma, optic atrophy) or optic disc drusen, or congenitally crowded optic discs.

OCT high-quality fundus images (line scanning ophthalmoscope, transverse resolution in tissue 25 μm) from all 24 patients (48 eyes) and 22 normal subjects (44 eyes) were reviewed by three masked observers. High definition (HD)-OCT images were mixed and shown randomly (figure1A). The observers were asked to classify each optic disc as being normal or showing PO, then to grade PO according to Modified Frisén Scale with a key feature (*) for each grade13.
Grade 0 (normal optic disc):
- Prominence of the RNFL at the nasal, superior and inferior poles in inverse proportion to disc diameter.
- Radial nerve fibre layer striations, without tortuosity.

Grade 1 (minimal degree of oedema):
- C-shaped halo that is subtle and greyish with a temporal gap: obscures underlying retinal details.*
- Disruption of normal radial nerve fibre layer arrangement striations.
- Temporal disc margin normal.

Grade 2 (low degree of oedema):
- Circumferential halo.*
- Elevation (nasal border).
- No major vessel obscuration.

Grade 3 (moderate degree of oedema):
- Obscuration of ≥1 segment of major blood vessels leaving disc.*
- Circumferential halo.
- Elevation (all borders).
- Halo (irregular outer fringe with finger-like extensions).

Grade 4 (marked degree of oedema):
- Total obstruction on the disc of a segment of a major blood vessel on the disc.*
- Elevation (whole nerve head, including the cup).
- Border obstruction (complete).
- Halo (complete).

Grade 5 (severe degree of oedema):
- Obstruction of all vessels on the disc and leaving the disc.*

The three observers were in agreement on disc grade in 94% of the eyes (86 images). Because the patients with optic nerves drusen or congenitally crowded optic discs were excluded from our study, there was no disagreement between grades 0 versus 1. One-grade differences were observed by one observer compared with the other two observers between grades 1 versus 2 in three eyes, 2 versus 3 in one eyes, 3 versus 4 in two eyes. For analysis, we considered only one eye for each individual. We selected the right or left eye of all 24 patients with PO and 22 normal subjects taking into account the agreement by grades of optic disc swelling between observers. This left a final 22 control eyes and 24 eyes with PO. Agreement by grades of optic disc swelling was 98%. If all three observers were not in agreement, grading by three observers was used, with the third reviewer’s grade excluded. We divided PO into two subgroups, mild PO (grade 1 and 2) (n=18) and moderate-severe PO (grade 3–5) (n=6).

Investigation
All patients and controls performed an OCT (Cirrus HD-OCT, software version 4.0.1.3; Carl Zeiss Meditec Inc, Dublin, USA). The HD-OCT is a non-contact, high-resolution tomographic and biomicroscopic imaging device. It is indicated for in vivo viewing, with axial cross-sectional and three-dimensional imaging and measurement of posterior ocular structures, including retina, RNFL, macula and optic disc. The line scanning ophthalmoscope provides an exquisite high-quality fundus images that reveals subtle details of pathology. The HD-OCT image is a high-definition cross-sectional view that has a transverse resolution of

![Figure 1](image_url)
25 μm. The HD-OCT B-scan has an axial resolution of 5 μm and a transverse resolution of 15 μm. The scan speed is of 27,000 A-scans per second. The HD-OCT uses performance segmentation and other image-processing algorithms to detect different layers of the retina and to map the thickness of different retinal layers.

In this study we evaluated and compared two methods of PO measurements using the HD-OCT (figure 2).

1. **RNFL thickness measurements** using the standard optic disc cube 200×200 acquisition protocol. The algorithm of this protocol measures the RNFL thickness between its anterior border (internal limiting membrane) and its posterior border (less reflective layer). Segmentation algorithms have been developed for the three-dimensional RNFL data set, in conjunction with the 3.4 mm-diameter circle section software. From the disc shape, the geometric centre is found and the A-scans forming a 3.4 mm-diameter circle that centre are selected to form a RNFL circular B-scan, similar to that acquired by the time domain OCT. Values for RNFL thickness obtained from each A-scan were averaged to find the overall average thickness as well as the average thickness for each of the quadrants (temporal, inferior, nasal and superior) (figure 2A).

2. **PTR thickness measurements** using the macular cube 512×128 acquisition protocol centred on the optic nerve head. The algorithm of this protocol defines the edges of the internal limiting membrane and the retinal pigment epithelium (ILM-RPE) and thus measures the total retinal thickness. Software for the HD-OCT, by using macular thickness analysis, allows correcting signals for ILM-RPE in the case of severe papilloedema if the RPE is difficult to observe. The reliability of the examinations was independent of the severity of the oedema due to the signal correction procedure. Retinal layer thickness values were calculated sectorally (temporal, superior, nasal and inferior) within three circles area: the innermost circle has a diameter of 1 mm, the middle circle has a diameter of 3 mm and the outer circle has a diameter of 6 mm (figure 2B). In this study, we only used the 3 mm-diameter circle, which is the first peripapillary circle area extending from the 1 to 3 mm circles. We excluded the central 1 mm circle, where RPE is obviously missing due to the presence of the optic canal. In addition, the 3 mm PTR circle area provides more measurements points than the 3.4 mm RNFL circle line.

**Statistical analyses**

Repeated-measures ANOVA was performed on the RNFL and PTR thickness values, either as an average or in each quadrant. One-way ANOVA was used to test the effect of group of subjects (control, mild PO, moderate-severe PO; between-subject factor) and the effect of quadrant (temporal, superior, nasal, inferior; within-subject factor) on the RNFL and the PTR thicknesses. Post hoc comparisons were performed using Scheffe test. A two-tailed p value of <0.05 was considered as statistically significant. All statistics were performed by the STATISTICA software package (Statistica 9, Statsoft Inc, Tulsa OK, USA).

**RESULTS**

**RNFL thickness measurements**

Average RNFL thickness in the moderate-severe PO, mild PO and control groups was 299.3±10.9 μm, 112.4±6.3 μm and 96±5.7 μm, respectively. The one-way ANOVA demonstrated an effect of group on the RNFL thickness (group effect, F (2, 43)=141, p<0.001). Average RNFL thickness values were significantly greater in the moderate-severe PO group than in the mild PO (p<0.001) and control groups (p<0.001). However, average RNFL thickness values were not significantly different in the mild PO group versus the control group (p=0.17). The two-way ANOVA showed an effect of group and of quadrant on the RNFL thickness (F (6, 129)=20, p<0.001). Although average RNFL thickness values were significantly greater in all quadrants in the moderate-severe PO group than in the mild PO (p<0.001) and control groups (p<0.001), there were no differences in RNFL thicknesses in the mild PO group versus the control group in each quadrant (temporal, p=1; superior, p=1; nasal, p=1; inferior, p=0.9) (Table 1). Figure 1B,C shows examples of RNFL thickness analysis in one subject from each of the three groups.

**PTR thickness measurements**

Average PTR thickness in the moderate-severe PO, mild PO and control groups was 804.5±17 μm, 463.1±9.8 μm and 352.4±8.9 μm, respectively. The one-way ANOVA demonstrated an effect of group on the PTR thickness (group effect, F (2, 43)=306, p<0.001). Average PTR thickness was greater in the moderate-severe PO group than in the mild PO group (p<0.001) and in the control group (p<0.001). Moreover, average PTR thickness was greater in the mild PO group versus the control group (p<0.001). The two-way ANOVA showed an effect of group and of quadrant on the PTR thickness (F (6, 129)=13, p<0.001). Eyes with mild PO compared with the control group show significantly greater PTR thickness values in each quadrant except the temporal (temporal, p=0.4; superior, p<0.0001; nasal, p<0.0001; inferior, p<0.0001) (Table 1). Figure 1D,E,F shows examples of PTR thickness analysis in one subject from each of the three groups.

**DISCUSSION**

This study showed that the PTR method was more sensitive than conventional RNFL thickness measurement in the detection of mild PO. Although the two techniques were equivalent to document moderate-severe PO, only PTR could differentiate patients with mild PO from controls. The greater sensitivity of the PTR method probably results from the fact it takes into account subretinal fluid accumulation that occurs in PO and in other various causes of optic disc swelling.14 8–12 Our findings confirm those from a recent study in which there was a stronger correlation of PO grade with total retinal thickness than RNFL thickness.13

Optic disc oedema in raised ICP is caused not only by intracytoplasmic swelling of ganglion cell axons secondary to axoplasmic transport stasis, but also by accumulation of interstitial fluid in the tissues of the optic nerve head.15 16

**Figure 2** (A) Optic disc cube 200×200 acquisition protocol used for retinal nerve fibre layer (RNFL) thickness measurements of fixed standard 3.4 mm-diameter circular scan; (B) macular cube 512×128 acquisition protocol centred on the optic nerve head in order to measure the peripapillary total retinal (PTR) thickness inside the 3.0 mm-diameter circle area.

In normal conditions, there is no leakage into the peripapillary subretinal space because of the barrier property of the intermediary tissue of Kuhnt. Disruption of Kuhnt tissue results in a leakage from the optic nerve head into the peripapillary subretinal space. Samuels et al showed that Kuhnt tissue was disrupted in the case of severe optic disc swelling. However, our findings suggest that even in mild PO there might be a peripapillary fluid leakage leading to total retinal thickening. Therefore, PTR thickening might occur before RNFL thickening. Based on this finding, we consider that the measurement of the PTR thickness would be a more sensitive and specific discriminator of PO than measurement of the RNFL thickness.

By means of measuring PTR thickness, our results demonstrate the potential usefulness of this method. This technology increases the sensitivity for detection of diseases such as PO and may be particularly valuable in specific clinical situations, such as in the case of subclinical PO, or PO associated with retinal nerve fibre atrophy caused by longstanding duration of PO. In the second case, the timing of the OCT in the clinical course may affect the interpretation of the RNFL results. The difference in the ability of RNFL and PTR thickness measurements to detect oedema will increase with the importance of RNFL atrophy. In the case of the optic disc atrophy, PO caused by accumulation of interstitial fluid in the tissues of the optic nerve head because of impossibility of atrophied ganglion cell axons to swell. Accordingly, the use of PTR thickness measurements in association with the RNFL thickness measurements enables discrimination between oedema and atrophy. However, our study was restricted to patients without optic disc atrophy.

Besides PE, PTR thickness measurements are useful for the diagnosis of optic nerve head drusen. In addition, Johnson et al have shown that OCT can differentiate optic disc oedema from optic nerve head drusen by means of quantitative comparisons of RNFL and subretinal hyporeflective space thickness.

Moreover, this technology could be useful in paediatric pathology due to the unavailability of the normative database for the RNFL measurements. There is no normative database for PTR thickness measurements in paediatric patients, but PTR thickening and subretinal hyporeflective space in the peripapillary region confirm the diagnosis of PO.

In addition, PTR thickness measurement is also a sensitive method for the monitoring of PO. In our study, the follow up was possible in some of our patients, and no disparity between resolution of RNFL and PTR thickening was noticed.

PTR thickness measurement would be an interesting tool to compare crowded optic discs with mild PO. These issues can be explored in further studies. The aim of our study was to propose a new and useful method for clinicians in the diagnosis of mild PO.

Our study has several limitations. Our sample size is small, although our results are unequivocal. The use of a 3 mm diameter circle area with a 1 mm diameter inner circle may not fully cover the RPE on its inner surface since the optic disc diameter may vary from 1 to 2 mm. However, the same procedure was used in the three groups studied, minimising the consequence of this bias. Comparing different protocols with different circle sizes is not ideal. In fact, the 5 mm PTR circle is not a line, but an area, which extends from the 1 to 5 mm circles and provides more measurements points than 5.4 mm RNFL circle line. Therefore, PTR circle area is more appropriate for oedema than the 5.4 mm RNFL circle line.

Our results emphasise the need to develop a specific acquisition protocol to assess the PTR measurement and to obtain normative data. Ophthalmologists should be aware that when using OCT RNFL scans that RNFL thickness values may be normal in patients with mild PO.

Competing interest None declared.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the local ethical committee (comité de protection des personnes), in agreement with the Declaration of Helsinki and the French Bioethics Laws.

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