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PEDIATRICS

Applicability of the ISNT and IST rules on retinal nerve fiber layer measurement on spectral-domain optical coherence tomography in normal Indian children

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Abstract
Background To determine the applicability of the ISNT (inferior>superior>nasal>temporal) and IST (inferior>superior>temporal) rules on retinal nerve fiber layer (RNFL) measurement on spectral-domain optical coherence tomography (SD-OCT) in normal children.
Methods A prospective, cross-sectional study including consecutive subjects between the ages of 5–18 years who were born at term (≥37 weeks gestational age) and with a normal birth weight (≥2500 g) presenting to the out-patient department for refractive error examination. RNFL measurement was done on Spectralis SD-OCT. Exclusion criteria were best-corrected visual acuity less than 20/20, spherical equivalent (SE)>± 5 diopter (D), applanation IOP >21 mmHg, cup-to-disc (C/D) ratio of >0.5, C/D ratio asymmetry of >0.2 between eyes and any retinal or optic disc anomaly as determined by mydriatic fundus examination. Subjects with amblyopia, strabismus, or family history of optic nerve or retinal disease were excluded. Poor cooperation for SDOCT imaging and lack of consent were other exclusion criteria.
Results The ISNT rule on the RNFL was followed only by 30 eyes (23.8 %), while the IST rule was followed by 66 eyes (52.4 %) ($p<0.001$). The superior RNFL was thicker than the inferior in 57 eyes (45.2 %) while the temporal RNFL was thicker than the nasal in 63 eyes (50 %). The age, gender, spherical equivalent, and disc size did not predict the followability of the ISNT and IST rules ($p>0.05$).
Conclusions The ISNT and the IST rules for RNFL are not universally followed by all normal eyes in children. All deviations should therefore not be considered pathological.

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Introduction

Glaucoma is characterized by a progressive degeneration of the retinal ganglion cells (RGCs) and their axons, leading to a reduction in the thickness of the retinal nerve fiber layer (RNFL) [1]. The RNFL forms the neuroretinal rim (NRR) as it leaves the eye in the form of the optic nerve. Jonas et al. [2] showed on disc photographs that the normal NRR follows a typical configuration in which the inferior NRR is the thickest, followed by the superior, nasal, and the temporal (ISNT rule), which is violated in glaucoma. Optical coherence tomography (OCT) has been widely used for diagnosis and follow-up of optic nerve and retinal disorders in children [3–5]. It allows objective measurement of the optic nerve head (ONH), retinal nerve fiber layer (RNFL) and macular thickness in a non-invasive manner [6]. Spectral-domain OCT (SD-OCT) is a further refinement of this technique which allows imaging with a faster scan rate and at a higher resolution [7, 8]. One important limitation for application of SD-OCT to children is the fact that a robust normative database does not exist for an age of less than 18 years. However, there have been some studies recently on deriving the normative for SD-OCT in children [9–14]. The applicability of the NRR rules in children has been tested before [15]. However, there are no studies that look into whether the classical ISNT (inferior>superior>nasal>temporal) rule is applicable to the RNFL in normal children on SD-OCT. Since the nasal rim is last to be affected in diseases such as glaucoma [16], we also tested the applicability of the IST rule (inferior>superior>temporal) on the RNFL. The purpose of the present study was to investigate the applicability of these rules on the RNFL measurement in normal children.

Methods

This was a prospective, cross-sectional study conducted at a tertiary care ophthalmic institute between January 2014 and June 2014. Consecutive subjects between the ages of 5–18 years who were born at term (≥37 weeks gestational age) and with a normal birth weight (≥2500 g) presenting to the out-patient department for refractive error examination were included in the study. A verbal consent was obtained from all subjects. An informed consent was obtained from the legal guardian of each participant. Additional written consent was obtained from all children who were at least 12 years old. The study protocol was prospectively approved by the institutional review board and health research ethics committee (Dr. TV Patel Eye Institute Ethics Committee).

The subjects underwent a full ophthalmic examination, including best-corrected visual acuity tested with age appropriate charts, cycloplegic refraction with cyclopentolate 1 % eye drops, intraocular pressure (IOP) measurement with Goldmann applanation tonometry (GAT), slit-lamp biomicroscopy, and fundus examination with indirect ophthalmoscopy. The OCT scanning for RNFL thickness was done using Spectralis OCT (Heidelberg Engineering, Carlsbad, CA, USA). All patient examination was performed by one of the authors (PD).

Exclusion criteria were best-corrected visual acuity less than 20/20, spherical equivalent (SE)>± 5 diopter (D), applanation IOP >21 mmHg, cup to disc (C/D) ratio of >0.5, C/D ratio asymmetry of >0.2 between eyes, and any retinal or optic disc anomaly as determined by mydriatic fundus examination. Subjects with history of ocular abnormalities

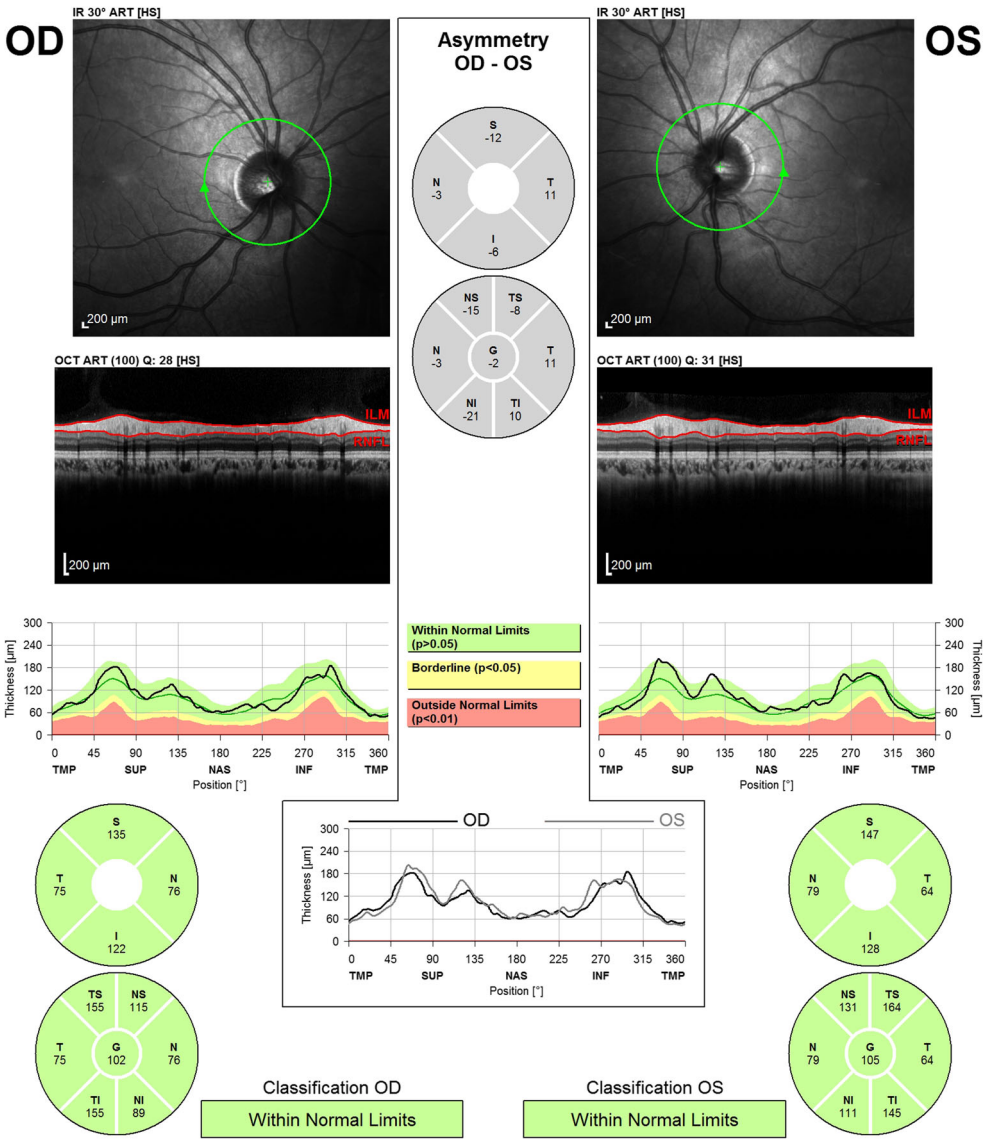

Fig. 1 A representative Spectralis optical coherence tomography retinal nerve fiber layer printout

including amblyopia, strabismus, or family history of optic nerve or retinal disease were excluded.

In addition, children who could not cooperate for the SD-OCT examination or whose parents did not provide consent were also excluded from the study.

OCT measurements

All images were acquired with the Spectralis SD-OCT (version 5.6.1) after pupillary dilation. The instrument has a scan speed of 40,000 A-scans per second, with a 12-degree diameter scan circle around the optic nerve. The scan circle diameter (mm) depends on the axial eye length of the eye, which is typically 3.5 to 3.6 mm. TruTrack image alignment software tracks for eye movement, and provides the ability to obtain multiple images from the exact same location.

All images were centered on the optic disc at the time of acquisition, and had a quality score of >25. Peripapillary RNFL thickness values were noted for the 4 quadrants: superior, temporal, inferior, and nasal (Fig. 1). The maximum vertical disc size was noted using the measuring tool on the Spectralis SD-OCT.

Statistical analysis

Descriptive and inferential statistics were performed using STATA version 12 for Windows (StataCorp LP, College Station, TX, USA). A p value <0.05 was considered statistically significant. Chi-square test was done to determine whether the difference in the followability of ISNT and IST rules was significant. Logistic regression analysis was done to see the effect of age, gender, SE, and disc size on the followability of the ISNT and IST rules.

Results

A total of 135 subjects were initially included. Nine subjects were unable to undergo SD-OCT imaging due to poor cooperation, and were excluded. Finally, 126 subjects completed the study. One eye of each subject was randomly selected for analysis by a random number table. This included 60 males and 66 females. The mean age of the participants was 11.42±3.59 years with a mean SE of −0.4±1.4 D. The age distribution of the participants is shown in Fig. 2. The mean GAT-measured IOP was 13.3±1.9 mmHg. The average vertical disc size and RNFL thickness were 1.7±0.6 mm and 100.3±8.3 microns respectively. Table 1 summarizes the patient demographics and RNFL measurements in all the 4 quadrants. The ISNT rule on the RNFL was followed only by 30 eyes (23.8 %), while the IST rule was followed by 66 eyes (52.4 %) (p<0.001) (Table 2). The superior RNFL was thicker than the inferior in 57 eyes (45.2 %) while the temporal RNFL was thicker than the nasal in 63 eyes (50 %). The age, gender, SE, and disc size did not predict the followability of the ISNT and IST rules on logistic regression analysis (p>0.05).

Discussion

Subjective tools for evaluation of optic nerve function such as the visual field examination in the pediatric population is difficult because of the lack of comprehension of the testing methodology, rapid boredom, distraction, and fatigue. There is a dire need for tools aiding objective assessment in this age group that are quick, reliable, reproducible, and less invasive. SD-OCT is one such diagnostic tool for assessing the RNFL.

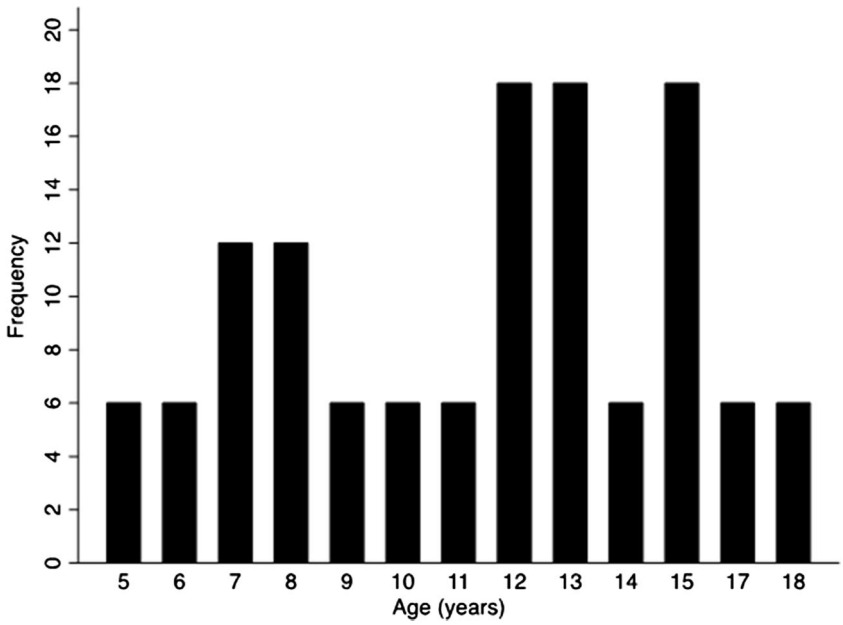

Fig. 2 Bar chart showing the age distribution

Table 1 Patient demographics and the retinal nerve fiber layer measurements

Age (years)	11.4±3.6
Gender (M:F)	60:66
SE (diopter)	−0.4±1.4
IOP (mmHg)	13.3±1.9
Disc size (mm)	1.7±0.6
Avgrnfl (microns)	100.3±8.3
Infrnfl (microns)	127.2±11.1
Suprnfl (microns)	125.2±18.3
Nasrnfl (microns)	74.8±13.8
Temprnfl (microns)	74.1±10.9
Inf–Sup diff (microns)	1.98±15.46 (range, −37 to 40)
Nas–Temp diff (microns)	0.76±20.78 (range, −31 to 69)

Abbreviations M male, *F* female, *SE* spherical equivalent, *IOP* intraocular pressure, *mm* millimeters, *mmHg* millimeter mercury, *Avgrnfl* average retinal nerve fiber layer, *Infrnfl* inferior retinal nerve fiber layer, *Suprnfl* superior retinal nerve fiber layer, *Nasrnfl* nasal retinal nerve fiber layer, *Temprnfl* temporal retinal nerve fiber layer, *Inf–Sup diff* difference between the inferior and superior quadrant nerve fiber layer thickness, *Nas–Temp diff* difference between the nasal and temporal quadrant nerve fiber layer thickness

The reproducibility for SD-OCT has already been established [17]. Serial changes in the OCT measurements may be an early sign of a disease. Knowledge of normal RNFL distribution pattern is therefore essential to avoid confusion with physiological variations. To the best of our knowledge, this is the first report on the applicability of NRR rules on the RNFL in children measured by SD-OCT.

The average RNFL measured in our study was 100.3±8.3 microns. This is similar to what is reported by other studies [10, 11]. The average quadrant-wise RNFL thickness reported in studies have shown great variation as regards to following the ISNT rule with a number of reports demonstrating exceptions [11, 13, 18–22]. Though the average-quadrant-wise RNFL thickness values in our study followed the ISNT rule, it was not so for the individual eyes. The ISNT rule on the RNFL was followed only by 30 eyes (23.8 %). These results are in contradiction to another study where the ISNT rule on the NRR was followed in 30 eyes (56 %) of children between 5 and 16 years of age [15]. However, this study was done on Heidelberg retinal tomography, and hence cannot be directly compared to the results of our study. Hwang et al. [23] studied the neuroretinal rim thickness on SD-OCT in adults and found that the ISNT rule was applicable only in 10/80 normal eyes (13 %). Another study by Pradhan et al. [24] showed that the ISNT rule on the RNFL in normal adults was followed by 89/189 (47.1 %) of the normal eyes. This study was however done on a Stratus time-domain OCT. The IST rule was better followed in our study with 66 eyes (52.4 %) obeying it. Similar results have also been found in adults by Pradhan et al., who demonstrated an increase in the followability of the IST rule as compared to the ISNT rule on the RNFL (58.7 % vs 47.1 % respectively). Rao et al. [11] in their study on Indian eyes showed that their average superior quadrant RNFL measurements were greater than the inferior. A similar paradox was also seen in the average nasal and temporal RNFL measurements, where the thickness in the temporal quadrant was more than the nasal. Leung at al. [22] also found that the average RNFL thickness in their study reduced from superior to inferior to temporal to nasal quadrants. In our study, the superior RNFL was thicker than the inferior in 57 eyes (45.2 %), while the temporal RNFL was thicker than the nasal in 63 eyes (50 %). Three eyes in our cohort had a temporal RNFL thickness greater than the superior. The RNFL thickness in all these three eyes reduced from inferior to temporal to superior to nasal quadrants. However, the difference between the temporal and superior RNFL thickness in all three eyes was modest, with a maximum difference of only 4 microns.

Table 2 Followability of the ISNT and IST rules

	Number of eyes (%)	
Rule	Yes	No
ISNT	30 (23.8 %)	96 (76.2 %)
IST	66 (52.4 %)	60 (47.6 %)

Abbreviations ISNT inferior>superior>nasal>temporal, *IST* inferior>superior>temporal

Logistic regression analysis in our study showed that the followability of the ISNT and IST rules were not affected by age, gender, SE or disc size ($p>0.05$). Alamouti et al. [25] studied the variation in the rate of RNFL decrease with age. They suggested that the reduction is slower in the younger age group which was the case in our study. Previous studies have found no relation of gender with the RNFL thickness [18, 21]. Salchow et al. [18] have shown an increase in the RNFL thickness with increase in hyperopia. Cheung et al. [26] similarly demonstrated a thinning of the RNFL with increased severity of myopia. We included only those children with SE within ±5 D. This would have eliminated high myopes and hyperopes in our study, thereby negating their effect on the measured RNFL thickness. All this explains why age, gender, and SE were not a significant predictor for followability of the ISNT and IST rules in our study. Though the Spectralis OCT scan diameter depends on the axial length, for a typical eye it is 3.5–3.6 mm in diameter. The optic disc size can influence the RNFL measurements, with a reduction in the measured RNFL thickness shown with increasing distance from the disc margin [27]. However, the potential error arising from it would likely affect the RNFL measurements in all quadrants, and therefore would not have changed the followability of the ISNT and IST rules in our study. Another study has shown that ISNT rule is increasingly not followed in large pediatric optic discs [28]. The average vertical disc size was 1.7±0.6 mm (range, 1.35–2.00 mm) in our study. It is perhaps because of the absence of large discs in our cohort that the disc size did

not significantly predict the followability of the ISNT and IST rules in this study ($p>0.05$). Our study is also limited by the fact that it involved Indian eyes only. Alasil et al. [29] have shown that racial differences exist while measuring the RNFL on SD-OCT. They reported thinner RNFL thickness values in Caucasians compared to Hispanics and Asians. Hence, the results of our study may not be applicable to a population with different ethnicities.

To conclude, the ISNT and the IST rules for RNFL are not universally followed by all normal eyes in children. All deviations should therefore not be considered pathological.

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