Original Article

Five year study confirms Retinal nerve fibre layer loss is the earliest structural evidence of Primary Open Angle Glaucoma

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Purpose: To evaluate whether peripapillary Retinal Nerve Fibre Layer thickness (RNFLT) loss as estimated by the Optical Coherence Tomography 3 (OCT 3)in patients labeled as glaucoma suspects, actually converted to Standard Automated Perimetry (SAP) changes within a study period of sixty months. To establish RNFLT loss as the earliest evidence of Primary Open Angle Glaucoma (POAG).

Design: Prospective Longitudinal study.

Participants: 732 eyes of glaucoma suspects

Methods: 732 eyes in the age group of 35 - 70 years attending the glaucoma service of a tertiary referral centre over a period of five calendar years were labelled as glaucoma suspects on the basis of BCVA of atleast 20/20 with ≤+5 or ≤-5 Dsph and ≤+2 or ≤-2 Dcyl. IOP ≥ 22mmHg (Central Corneal Thickness-within normal limits). Asymmetrical Cupping > 0.2 difference in two eyes or >0.6 in either eye. Open angles on gonioscopy. Transparent ocular media. Humphrey Visual Field Analysis – within normal limits (24-2 Full Threshold).

All 732 eyes who met the inclusion criteria were subjected to SAP(24-2 Full Threshold) every 3months and RNFLT analysis –peripapillary 3.4mm circular scans by the OCT3 every 3months.Abnormal SAP was defined as 4 points depressed at p<5% or a cluster of 3 points depressed at p<1%.RNFLT loss was defined as ≥1 quadrant abnormal at the <5% level or ≥1 clock hour abnormal at the <1% level

Correlations between deviation from normal (thinner than 95% of normal) RNFLT measurements taken at 30° sectors (12 sectors described as clock hours) and SAP average Pattern Deviation of 21 VF zones were determined. The number of OCT measured RNFL sectors outside normal limits and the number of VF zones outside normal linits were also compared.

Main Outcome Measures: Humphrey Visual Field Analysis – within normal limits (24-2 Full Threshold)

Results: 732 eyes divided into 4 groups

Group α – 674 eyes had RNFLT loss. **Group β** – 596 eyes had RNFLT loss & converted to abnormal SAP. **Group γ**– 48 eyes had no RNFLT loss. **Group δ** – 10 eyes converted to abnormal SAP without RNFLT loss. **Chi square test** showed **Group α :Group β (p<0.01).Group γ :Group δ (p>0.05)** Statistically significant number of glaucoma suspects with RNFLT loss converted to SAP abnormalities (p<0.01) RNFL areas most frequently outside normal limits were inferior & inferior temporal regions. Most sensitive RNFL area was Inferior quadrant. Least sensitive VF zone was superior hemifield. OCT sectors 6,7, & 8 o'clock hours best correlated with SAP pattern deviation VF zones 13,14 &16. RNFLT loss measured by OCT 3 is topographically correlated with glaucomatous VF defects measured with SAP. Conversion time from detection of RNFLT loss was 36.4 – 60.8 months. Average lead time 48.6 months.Most relevant index — of the 454 eyes with RNFLT loss,the number of converters were 346. Positive Predictive value for OCT 3 was 88%.

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Conclusions: Structural assessment using the OCT3 provides reproducible quantitative measurements. OCT could be useful in detecting Pre-perimetric glaucoma and therefore earlier commencement of treatment can prevent visual loss.Monitoring of Glaucoma progression over an extended period would arrest continued injury. The study would be of clinical relevance to prevent visual loss in Primary open angle glaucoma.

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Introduction

The early diagnosis of glaucoma and the early detection of glaucomatous progression are twin central challenges facing ophthalmologists. Since glaucomatous damage is irreversible, prevention of this injury before it occurs is the essential strategy available to those treating this disease.Standard Automated Perimetry, which is unarguably the Gold Standard to evaluate glaucomatous neuropathy and to monitor disease progression has poor sensitivity for detecting glaucoma. Quigley and co workers showed that significant axonal loss may precede the development of visual field defect and identifiable cupping. Since the test requires subjective input, it is therefore prone to short and long term fluctuation, therefore, clearly there is a compelling need for more sensitive glaucoma diagnostic tests.

Work during the past two decades has resulted in the development and implementation of several imaging technologies designed to detect glaucomatous neuropathy at early stages of the disease. Structural assessment using the Stratus OCT provides reproducible and quantitative measurements. It could be useful in detecting pre-perimetric glaucoma, thereby allowing earlier commencement of treatment and preventing visual loss. In addition, monitoring of glaucomatous progression with OCT over an extended period of time could arrest continued injury to the Optic nerve.

Patients and Methods

The study series design of 732 eyes of patients aged 30 - 70 years were recruited from the out patient department of a tertiary referral centre, and labeled as glaucoma suspects on the basis of :

IOP ≥ 22mmof Hg
After instillation of topical corneal anaesthesia (propacaine hydrochloride 0.5% with Fluorescein sodium 1 mg) IOP was measured using the Goldmann Applanation tonometer

Central Corneal Thickness WNL
CCT was measured using an Ultra sound Pachymeter

Open Angles on Gonioscopy
Gonioscopy was done in dim illumination using a narrow slit beam not extending onto the pupillary area with Goldman's single mirror goniolens . The angle was graded using Shaffer's grading system. If no trabecular meshwork is seen in more than 180 degrees then that is considered to be occludable.

Asymmetrical Cupping
> 0.2 in two eyes or > 0.6 in either eye

Optic Disc Evaluation was done using a +90D lens at the slit lamp

Transparent Ocular Media
All eyes needed to have a clear media

Humphrey protocol 24-2 Threshold Test
within normal limits

B.C.V.A.
at least 20/20 (Refractive error ≤ ± 5D Spherical & ≤ ±2D Cylindrical)

All 732 eyes fulfilling the inclusion criteria were subjected to:

- SAP: humphrey full threshold 24-2 protocol
- OCT – peripapillary 3.4 mm circular scans for RNFL thickness

Standard Automated Perimetry was done using the 24-2 Threshold protocol of the Humphrey Visual Field Analyser 750 series. Fields were repeated every 3 months.

Abnormal SAP was defined as 4 points depressed at P<5% OR a cluster of 3 points depressed at P<1%.

SAP average Pattern Deviation of 21 VF zones were determined

2 repetitive SAP fields were considered to avoid false positives.

An increase of more than 1.66 D in the Pattern Standard

Deviation (PSD) of the overview printout, over the last test was labeled as progression.

RNFL thickness analysis was done using the Stratus OCT 3.4mm peripapillary scans were used and the RNFL analysis protocol was used. Scans with signal strengths 5 or more were considered. Serial analysis of the machine was used to identify progression.

The test was repeated every 3 months.

RNFL thickness was loss defined as

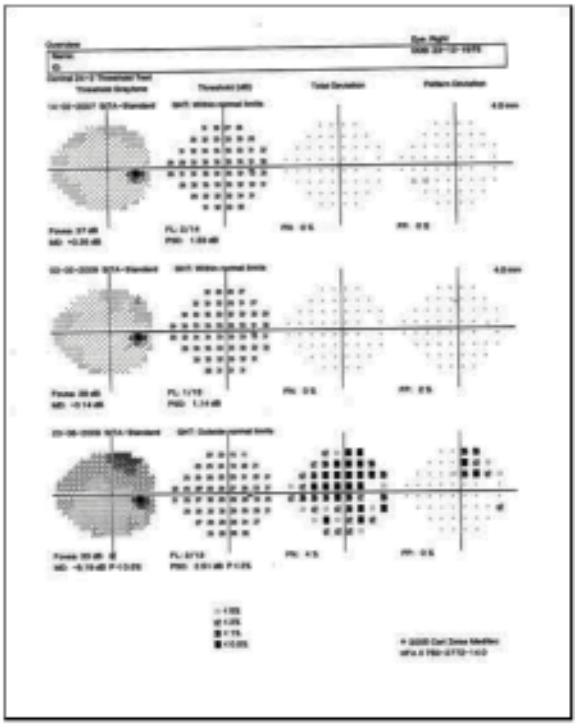
- ≥ 1 quadrant abnormal at <5% level OR
- ≥ 1 clock hour abnormal at <1% level
- Corelations Between RNFLT – 12 Sectors And SAP Average Pattern Deviation of 21visual Field Zones Were Determined
- Number of RNFL Sectors Outside Normal Limits Were Compared With Number of VF Zones Outside Normal Limits.

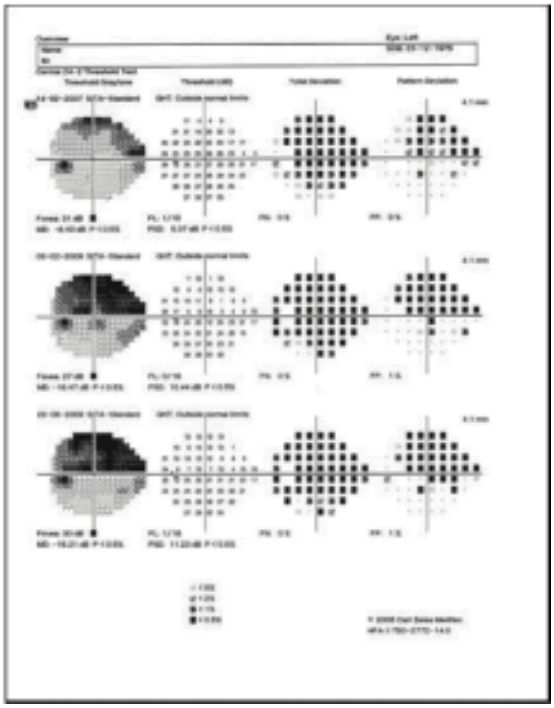
Results

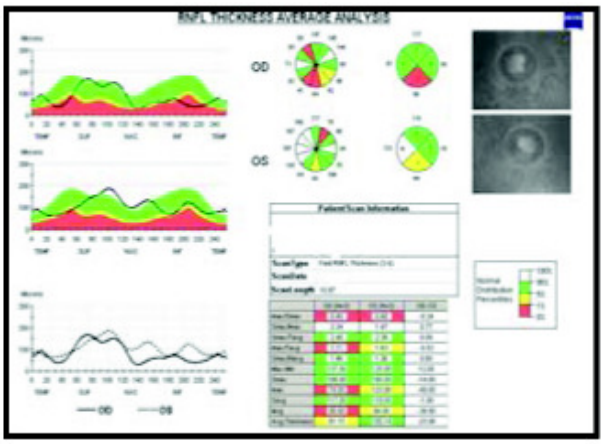
732 eyes were divided into 4 groups :

Group α consisted of 674 eyes which had RNFLT loss. **Group β** consisted of 596 eyes which had RNFLT loss & converted to abnormal SAP. **Group γ** consisted of 48 eyes with no RNFLT loss and **Group δ** consisted of 10 eyes which converted to abnormal SAP without RNFLT loss. **Chi square test** showed **Group α :Group β - a p value of p<0.01 and Group γ :Group δ a p value of p>0.05.** Therefore, a statistically significant number of glaucoma suspects with RNFLT loss converted to SAP abnormalities (p<0.01) RNFL areas most frequently outside normal limits were inferior & inferior temporal regions. Most sensitive RNFL area was Inferior quadrant. Least sensitive VF zone was superior hemifield. OCT sectors 6,7, & 8 o'clock hours best correlated with SAP pattern deviation VF zones 13,14 &16. RNFLT loss measured by OCT 3 is topographically correlated with glaucomatous VF defects measured with SAP. Conversion time from detection of RNFLT loss to development of visual field defect was 36.4 to 60.8 months. Average lead time was 48.6 months. The most relevant index was that of the 454 eyes, which showed RNFL loss,346 converted to SAP changes.Therefore, the Positive Predictive value for the OCT 3 was 88%.

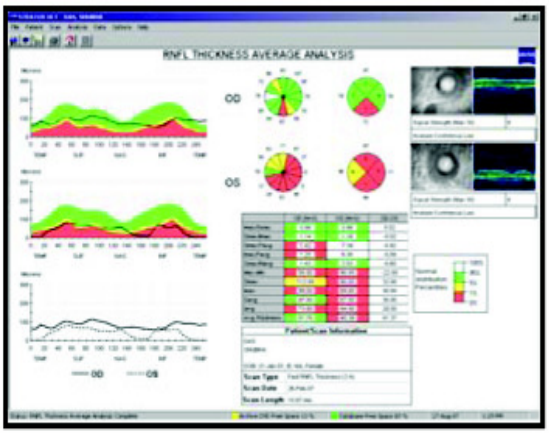
Converter







14 July, 2006



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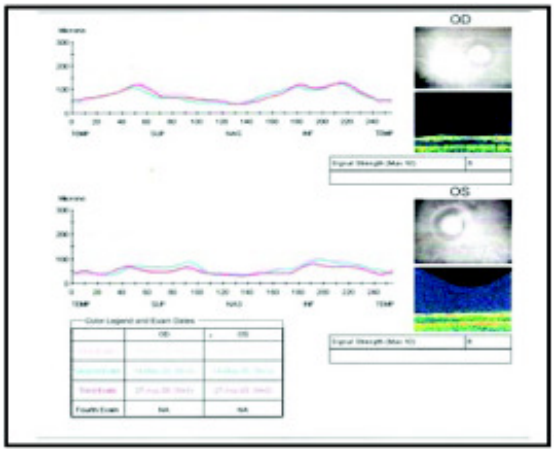

Serial Analysis of RNFLT

The Peripapillary OCT RNFL Thickness Data Analysis Quadrant Wise

Groups of Glaucoma suspects	Average	Superior	Supero-temporal	Temporal	Infero-temporal Ψ	Inferior Ψ	Nasal
(α) RNFL LOSS (n=674eyes)	110±12	125±14	130±15	90±16	105±12	85±12	82±16
(β)Converters with RNFL loss (n=596 eyes)	110±12	115±16	115±12	86±22	90±15	80±16	80±16
(γ) NO RNFL LOSS (n=48 eyes)	135±14	155±15	155±17	92±18	130±14	140±20	82±20
(δ) Converters without RNFL loss (n=10 eyes)	135±14	155±15	155±17	92±18	130±14	140±20	82±20

ψ Statistically significant between RNFLT & abnormal SAP (P< 0. 01)

Results

RNFLT SAP Analysis Results

Abnormal SAP	RNFLT loss 1 quadrant	RNFLT loss 1 clock hr	RNFLT loss >1 quadrant	RNFLT loss >1 clock hr	No RNFLT loss
4 points	82	0	178	107	6
3 points	74	0	172	109	4

Pie Chart showing RNFLT data analysis

732 eyes divided into 4 groups

Group α – 674 eyes had RNFLT loss
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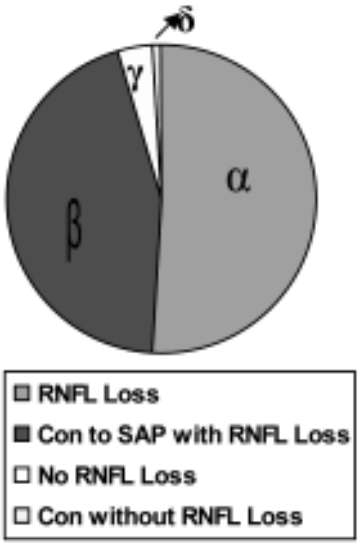
Group δ – 10 eyes converted to abnormal SAP without RNFLT loss

Group α :Groupβ ($p<0.01$)
Group γ :Group δ ($p>0.05$)



Conclusions

From the study results it was inferred that :

- Statistically significant number of glaucoma suspects with RNFLT loss converted to SAP abnormalities
- RNFL areas most frequently outside normal limits were inferior & inf temporal regions
- Most sensitive RNFL area was the Inferior quadrant. Least sensitive VF zone was the superior hemifield
- OCT sectors 6,7, & 8 o'clock best correlated with SAP pattern deviation VF zones 13,14 &16
- RNFLT loss measured by OCT 3 is topographically correlated with glaucomatous VF defects measured with SAP
- Conversion time from detection of RNFLT loss to development of visual field defects was 36.4 to 60.8 months. Average lead time was 48.6 months.
- Of the 454 eyes with RNFLT loss,the number of converters were 346. Therefore the Positive Predictive value of the Stratus OCT was 88%.

The principal finding of the study is that a statistically significant number of glaucoma suspects with RNFLT loss converted to SAP abnormalities($p< 0.01$).The Positive Predictive Value of 88% for early detection of glaucoma by the OCT 3 is a relevant index and confirms RNFLT loss precedes SAP changes and could therefore be used for earlier commencement of treatment to prevent visual loss.

Discussion

Cesar A Sanchez-Galeana[9] et al reported RNFLT loss measured with OCT3 is topographically correlated with glaucomatous VF defects measured with SWAP. Joel.S.Schuman[6,10] et al - pilot study reported VF defects were strongly related to thinner NFL($p=0.0001$).Inferior VF

defects correlated with thinner superior NFL, while superior defects were associated with thinner inferior NFL.Our study showed similar association between RNFL and VF. El Beltagi[8] TA et al reported- Linear regression results (R(2)) showed deviation from normal RNFLT at OCT3 clock hour positions 6 o'clock, 7 o'clock, and 8 o'clock (inferior and inferior temporal) was best correlated with SAP pattern deviation in visual field zones corresponding to superior arcuate and nasal step regions. Our study is consistent with this knowledge.

Nouri-Mahdavi K et al reported the sensitivity of OCT for detection of glaucoma to be 71%.Our Positive Predictive value is 88%.

Therefore RNFLT loss is the earliest evidence of Primary Open Angle Glaucoma , the understanding of this can be used for earlier detection of the disease and thus prevent visual loss.

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