Quantification of retinal nerve fiber layer changes in optical coherence tomography images reveals differential progression of glaucomas

Saumyadipta Pyne, Mohammad Hasnat Ali1, Meghana Aruru2, Harsha L Rao3

Abstract:

BACKGROUND: For monitoring the progression of glaucoma, a major cause of irreversible blindness, clinicians measure retinal nerve fiber layer (RNFL) changes in the eye.

MATERIALS AND METHODS: Based on a clinical cohort of patients, we computed the temporal differences in the RNFL patterns in their glaucomatous eyes using optical coherence tomography (OCT) images. To gain insights into disease progression, we quantified the precise changes in the RNFL clock-hour sector phenotypes in each glaucomatous eye between the first and second clinical visits.

CONCLUSION: Further, we identified 2 groups of patients using unsupervised clustering based only on their initial RNFL phenotypes, which may be investigated further to develop clinically useful models for prediction of glaucoma progression.

Keywords: Clustering, disease progression, glaucoma, optical coherence tomography, retinal nerve fiber layer phenotypes, cosine distance

Globally, glaucoma is the most common cause of irreversible blindness and the second leading cause of blindness.[1] Glaucoma is a chronic progressive optic neuropathy associated with the loss of retinal ganglion cells, resulting in permanent visual field (VF) loss and irreversible blindness. As damage to the retinal ganglion cells cannot be detected clinically, clinicians often rely on indirect methods such as changes in the retinal nerve fiber layer (RNFL). Visible, localized RNFL defects are often considered an early sign of glaucoma and are associated with neuronal losses, thereby making these structural observations more relevant in documenting the early changes in glaucoma.[4] RNFL changes in glaucoma may be present with or without VF loss.[3]

Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) are the two most common forms of primary glaucoma worldwide. Intraocular pressure (IOP) is the most important risk factor for the development and progression of glaucoma.[1,4] The two most commonly used diagnostic tests to detect glaucoma and determine its severity are the standard automated perimetry (SAP), which tests the VF loss and the optical coherence tomography (OCT), which evaluates structural changes in the RNFL. OCT is a widely used noninvasive imaging technology that uses low-coherence light to capture in vivo two- and three-dimensional images of the eye at micrometer resolution. Numerous studies have reported excellent diagnostic abilities of OCT-measured RNFL changes to discriminate glaucomatous eyes from normal eyes.[5,6]

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However, perhaps, the most challenging aspect of managing glaucoma is the ability to predict the course of progression of the disease. RNFL evaluation remains by far the most promising protocol for glaucoma detection and monitoring progression. In this direction, the calculation of precise changes in RNFL patterns as captured by longitudinal measurements of OCT could be particularly insightful since glaucoma is a slowly progressing disease. In the present study, based on a clinical cohort, we explore a new computational approach based on the well-known cosine distance to quantify the temporal changes in RNFL patterns across the clock-hour sectors in OCT data in glaucomatous eyes. Further, our unsupervised clustering of the initial RNFL patterns showed its potential utility for distinguishing early the groups of patients that undergo differential disease progression.

Materials and Methods

Data

The dataset was acquired from an ongoing, prospective, longitudinal study at Narayana Nethralaya, a tertiary eye care center in Bengaluru in Southern India. Written informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Narayana Nethralaya. Participants of the study, all of the Indian ancestry, include glaucoma patients (POAG and PACG subtypes), glaucoma suspects who are longitudinally evaluated every 6–12 months with SAP, optic disc stereo photographs, and OCT for the detection of progression.

POAG patients had open angles on gonioscopy and glaucomatous changes on optic nerve head (ONH) examination (neuroretinal rim narrowing, notching, and RNFL defects) as documented by glaucoma experts on dilated examination and confirmed by the masked evaluation of stereoscopic optic disc photographs by graders. PACG patients had occludable anterior chamber angles on gonioscopy, presence of goniosynechiae, a history of IOP >21 mm Hg, and had undergone laser peripheral iridotomy before the study inclusion. The anterior chamber angle was examined using an indentation gonioscope and was considered occludable if, in primary position, the posterior trabecular meshwork was not seen in three or more quadrants. [9] Pretreatment IOP or VF loss was not used to define POAG and PACG.

The inclusion criteria for all participants included age ≥18 years, corrected distance visual acuity of 20/40 or better, and refractive error within ± 5 D sphere and ± 3 D cylinder. The exclusion criteria included the presence of any media opacities that prevented good quality OCT scans or any retinal or neurological disease other than glaucoma, which could confound the evaluation. All participants underwent a comprehensive ocular examination, which included corrected distance visual acuity measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic optic disc photography, VF examination, and OCT imaging with Cirrus HD-OCT (model 5000, Carl Zeiss Meditec Inc., Dublin, CA, USA) every 6–12 months.

OCT examination was conducted using 200 × 200 ONH cube scan protocol on Cirrus HD-OCT which uses a superluminescent diode laser with a center wavelength of 840 nm at an axial resolution of 5 µm. The ONH protocol is based on a tridimensional scan of a 6 × 6 mm² area centered on the optic disc where information from a 1024 (depth) × 200 × 200-point parallelepiped is collected. RNFL thickness was calculated along a circle 3.46 mm in diameter, positioned evenly around the center of the optic disc. The calculation circle was also divided into smaller 12 clock-hours sectors of 30° each, and RNFL thickness in each of the 12 clock-hours sectors was measured. Image quality was assessed for all OCT scans. Poor quality images, which were defined as those with signal strength <6 or images with motion artifacts and segmentation errors, were excluded from the analysis.

Thus, for the present study, we obtained OCT RNFL data for glaucomatous eyes of n = 29 patients, along with their clinical covariates. The cohort consisted of 6 (21%) female and 23 (79%) male patients with 18 (68%) POAG and 11 (32%) PACG subtypes. Their baseline clinical measurements are described in Table 1.

Analysis

In the present study, we used cosine distance, an known method in linear algebra for measuring distances between a pair of vectors, to compute the differences in RNFL thickness phenotypes [a_i, j] for the ith glaucomatous eye [i = 1… N] across the 12 OCT clock-hour sectors j [j = 1…12] between the first and second clinical visits.

| Clinical variables | Mean±SD |
|-------------------|---------|
| Age (years)       | 60.73±9.81 |
| Rim area (mm²)    | 0.87±0.27 |
| Disc area (mm²)   | 2.09±0.37 |
| Average cup-to-disc ratio | 0.75±0.11 |
| Average thickness (µm) | 75.66±15.93 |
| Vertical cup-to-disc ratio | 0.75±0.12 |
| Cup volume (mm³)  | 0.59±0.36 |
| Disc diameter (mm) | 1.58±0.14 |
| Central corneal thickness (µm) | 527.7±55.77 |
| Highest untreated IOP (mmHg) | 19.31±3.69 |
| SAP mean deviation (dB) | −7.66±7.71 |

SD=Standard deviation, IOP=Intraocular pressure, SAP=Standard automated perimetry
at time-points \( t \mid t = 1, 2 \). Note that \( a_{i,j,t} \geq 0 \) for all values of \( i, j, t \).

The cosine distance \( d_{ew} \) between a given pair of eyes \( e, e' \) (samples indexed \( i \) and \( i' \) respectively), in terms of their OCT clock-hour phenotypes \( \{a_{i,j,t} \mid j = 1 \ldots 12\} \) and \( \{a_{i',j,t'} \mid j = 1 \ldots 12\} \) measured during time-points \( t \) and \( t' \), is defined as follows:

\[
d_{ew}(e, e') = \frac{2}{\pi} \times \cos^{-1}\left( \frac{\sum_{j}^{12} a_{i,j,t} a_{i',j,t'}}{\sqrt{\sum_{j}^{12} a_{i,j,t}^2} \sqrt{\sum_{j}^{12} a_{i',j,t'}^2}} \right).
\]

Thus, at a fixed time point the distance between two eyes \( e, e' \) is given by

\[
d_{ew}(e_i, e_i') = \frac{2}{\pi} \times \cos^{-1}\left( \frac{\sum_{j}^{12} a_{i,j,t} a_{i',j,t'}}{\sqrt{\sum_{j}^{12} a_{i,j,t}^2} \sqrt{\sum_{j}^{12} a_{i',j,t'}^2}} \right)
\]

and the distance for a fixed eye across two time points \( t \) and \( t' \):

\[
d_{ew}(e_i, e_i') = \frac{2}{\pi} \times \cos^{-1}\left( \frac{\sum_{j}^{12} a_{i,j,t} a_{i',j,t'}}{\sqrt{\sum_{j}^{12} a_{i,j,t}^2} \sqrt{\sum_{j}^{12} a_{i',j,t'}^2}} \right)
\]

For unsupervised learning of groups in RNFL clock-hour sector phenotype data, we used agglomerative hierarchical clustering (implemented in R by the “hclust” function) using the matrix of cosine distances \( \{d_{ew}(e_i, e_i')\} \) between the RNFL phenotypes of the glaucomatous eyes \( (e, e') \) of each pair of \((n = 29)\) patients as measured by OCT during their first clinical visit (at time \( t \)).

In addition, we computed the intervisit phenotypic difference in terms of the cosine distance \( D = d_{ew}(e_i, e_i') \) between the RNFL clock-hour sector data for each patient’s glaucomatous eye \( e \) as measured by OCT during the first and the second clinical visits at time-points \( t \) and \( t' \) respectively. The mean duration between these visits is 10.01 months (SD = 7.69). The median \((M = 0.059)\) of these \((n = 29)\) values of \( D \) were used to define two groups of patients: (i) “LowDiff” consisting of those with intervisit difference of RNFL phenotypes \( D < M \) and (ii) “HighDiff” containing the rest, i.e., for \( D \geq M \). Illustrative examples of intervisit RNFL phenotypic differences are shown in Figure 1.

**Results**

To gain insight into disease progression, each patient’s inter-visit RNFL phenotypic change was calculated with cosine distance \( D = d_{ew}(e_i, e_i') \) as described in the methods section. This allowed us to the identify groups with low and high intervisit differences, namely LowDiff and HighDiff. Interestingly, we observed statistical variations in certain features of their glaucomatous eyes. For instance, the distributions of the baseline optic disc diameter measurements of these two groups while overlapping have distinct shapes and modes [Figure 2].

This motivated us to ask the question as to whether the existence of groups of patients who may go on to progress in their disease differently could be predicted with early signatures in their RNFL phenotypes as captured in OCT data from their first clinical visit. To address this problem, we conducted unsupervised learning of patient groups using agglomerative hierarchical clustering of the “early” RNFL clock-hours phenotypes of the glaucomatous eyes based only on their first OCT data and using no other covariates. Notably, the clustering dendrogram based on cosine distances between every pair of glaucomatous eyes in our data reveals the clear existence of two clusters of early RNFL phenotypes (as shown in green and orange) in Figure 3.

Interestingly, we noted a statistically significant overlap between the two clusters identified in an unsupervised analysis based only on the early phenotypes, and the two groups of patients defined as HighDiff and LowDiff based on disease progression. Fisher’s exact test [with \( 2 \times 2 \) table shown in Figure 4] gives the \( P \) value (for odds of HighDiff for cluster 2) as 0.045. In contrast, the same test showed no statistically significant overlap between the same two clusters and the two subtypes of glaucoma patients (POAG and PACG).

**Discussion**

Glaucoma affects 1-in-200 individuals aged 50 years and younger and 1-in-10 individuals over the age of
It is estimated that 11 million individuals will be affected by glaucoma by the year 2020. It is, therefore, of critical importance to develop accurate and rigorous statistical models that can predict the progression of glaucoma for a given patient as early as possible following his/her diagnosis. In the present study involving the comparison of changes in RNFL phenotypes in glaucomatous eyes, our computational approach to quantify the changes in the clock-hour sector patterns illustrates the potential use of such objective means to capture the diversity in complex phenotypes and obtain early insights into disease progression.

In our future work, we plan to extend the power of our study with larger samples sizes and more time points to further explore these findings. It might be possible to validate our quantified differences in OCT RNFL phenotypes in glaucoma against genotypic and transcriptomic variations in a larger cohort. With more time points, we can study the effects of duration of time on RNFL phenotypic changes as well as the variability of such measurements across visits. Finally, given the inherent richness of the OCT data, we believe that new statistical models that can address the rich spatio-temporal dynamics and the complexity in the circular space of intraocular phenotypes need to be developed.

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**Conflicts of interest**
There are no conflicts of interest.

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