Review Article

Evaluating the Optic Nerve and Retinal Nerve Fibre Layer: The Roles of Heidelberg Retina Tomography, Scanning Laser Polarimetry and Optical Coherence Tomography†

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Abstract

Introduction: For many years, ophthalmologists have looked at the optic nerve head to evaluate the status of glaucoma. Clinical examination of the optic nerve head and retinal nerve fibre layer (RNFL) is however, subjective and sometimes variable. Recent developments in computer-based imaging technologies have provided a means of obtaining quantitative measurements of the optic nerve head topography and peripapillary retinal nerve fibre layer thickness. Methods: Multiple searches using Medline were carried out. Additional searches were made using reference lists of published papers and book chapters. Results: Studies involving three imaging technologies namely, confocal scanning laser ophthalmoscopy, scanning laser polarimetry and optical coherence tomography were reviewed. Overall, these technologies were reproducible and demonstrate good sensitivity and specificity in the range of 70 to 80%. Inclusion of age and ethnicity normative database will make these technologies more effective in screening and diagnosis. Quantitative measurements provide useful parameters for monitoring of patients. Conclusion: There is no consensus on the best technology for assessing structural damage in glaucomatous optic neuropathy. Therefore, as with any investigation, the clinician should exercise clinical correlation and judgment before instituting the appropriate treatment.

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Key words: Glaucoma, Imaging, Ophthalmoscopy, Optic neuropathy, Topography

Introduction

Glaucoma is an optic neuropathy with characteristic optic nerve damage and visual field loss. With the introduction of the ophthalmoscope by Helmholtz in 1851, ophthalmologists were able to visualise changes of optic nerve head associated with glaucoma. Von Graefe described glaucomatous optic nerve damage as "amaurosis with excavation of the optic nerve". Later works improved our understanding that glaucoma is a disease of the optic nerve and is associated with nerve fiber loss.

The diagnosis of glaucoma can sometimes be difficult. A two-prong approach is required during the assessment for damage, that in detecting structural changes in the optic nerve and determining functional loss in the visual field. For many years, ophthalmologists have looked at the optic nerve head to evaluate the status of glaucoma. In addition, landmark studies by Sommer and Quigley have shown that retinal nerve fiber defects precede visual field loss and therefore, examination of the retinal nerve fiber layer may yield important diagnostic information.[1,2]

Clinical examination of the optic nerve head and retinal nerve fibre layer (RNFL) is however, subjective, qualitative and variably reproducible. There is wide inter-observer and sometimes, intra-observer variability in between different examinations.[3] Accurate and objective methods of detecting disc and RNFL abnormalities, and their progression, would facilitate the diagnosis and monitoring of glaucomatous optic neuropathy.

Stereoscopic optic nerve head photography is a simple and low-cost method that is extremely useful to the clinician. It allows a 3-dimensional and permanent recording of the optic nerve head appearance. The interpretation of conventional photography however, remains subjective and differences sometimes arise even amongst experts examining the photographs on issues pertaining to discrimination between normal and abnormal discs.[3]

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Furthermore, the technique of acquiring the photographs may be difficult in patients with small pupils and media opacities.

The development of optic nerve head analysers such as the Glaucoma-scope (Ophthalmic Imaging Systems, Inc, Sacramento, CA) was an early attempt to provide a quantitative assessment of optic nerve head and peripapillary topography.[4] This technology using computer raster stereography technique to determine the depth of the disc was however limited by variability and poor resolution of images.

In recent years, innovations in computer-based ocular imaging technologies utilising the optical properties of the optic nerve and retinal nerve fiber layer provide a potential means of obtaining quantitative measurements of the optic nerve head topography and RNFL thickness. These technologies employ the use of lasers and exhibit some of the characteristics of a good diagnostic tool such as high sensitivity and specificity, good reproducibility, ability to detect change over time, simplicity in usage and interpretation and convenience for both patient and doctor.

Confocal scanning laser ophthalmoscopy is a technology, which is available commercially in an instrument known as the Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany,). Upon acquisition of a series of 32 optical coronal sections of the optic nerve, it generates a colour-coded topographic map of the optic nerve head. This allows the examiner to have a quantitative 3-dimensional assessment of the optic nerve head.[5-7]

Scanning laser polarimetry is a technology embodied in the GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies, Inc., San Diego, CA). It is a confocal scanning laser ophthalmoscope with an integrated polarimeter, which evaluates the thickness of the RNFL by utilizing the birefringent properties of nerve fibers.[8-10] As polarised light passes through the RNFL and is reflected back from the deeper layer, it undergoes a phase shift. This change, referred to as "retardation" is linearly correlated to the thickness of the polarizing medium, and is computed to give an index of RNFL thickness.

Optical coherence tomography (OCT, Zeiss-Humphrey Systems, Dublin, CA) is a new, noninvasive, noncontact, imaging technology which can image retinal structures in vivo with a resolution of 10 to 17 microns.[11,12] It is analogous to B-scan ultrasonography except that light wave instead of sound wave is used. Cross-sectional images of the retina are produced based on the temporal delay of back-scattered low coherence near infrared light (840 nm) from the retina and a reference mirror. The anatomic layers within the retina can be differentiated (Fig. 1) and the retina and RNFL thickness can be measured. Measurements of the RNFL in patients with glaucomatous optic neuropathy demonstrate good correlation with known properties of optic nerve head structure and visual function.[10,13] OCT has also been demonstrated to provide useful information in patients with macular oedema, macular hole, epiretinal membrane, central serous retinopathy, congenital pits of the optic nerve head, optic nerve head drusen, and macular degeneration.

Confocal Scanning Laser Ophthalmoscopy

The Heidelberg Retina Tomograph (newest version, HRT II; Heidelberg Engineering, Heidelberg, Germany) is a confocal laser scanning microscope for acquisition and analysis of 3-dimensional images of the posterior segment. It enables quantitative assessment of retinal and optic nerve head topography and precise follow-up of topographic changes. The HRT uses a 670 nm diode laser beam to scan the retina in a raster-like fashion. The presence of a confocal aperture ensures that only light originating from a particular plane is captured at any point in time. Planes which are out of focus are blocked by the aperture and do not reach the detector.

Thirty-two consecutive 2-dimensional coronal section images, each at a fixed focal plane equidistant to one another are acquired from the anterior portion of the optic nerve head to the retrolaminar portion. Each image contains 256 x 256 pixels, with each pixel representing the retinal height at that location relative to the focal plane of the eye. Stacking these images together layer-by-layer results in a 3-dimensional image. The (retinal) surface height at each point is computed; resulting in a matrix of height measurements that is visualised as the topography image. This allows quantitative assessment of the 3-dimensional properties of the retinal/optic nerve surface.

A standard reference plane is established. This plane is parallel to the peripapillary retinal surface and is located 50 microns posterior to the retinal surface in a temporal segment between 350 degrees and 356 degrees. The operator outlines the optic disc margin. This outline of the disc is known as the contour line. The reference plane serves as a boundary between the neural rim and cup. Tissue within the optic disc margin and above the reference plane is considered to be the neural rim. Tissue within the disc margin and below the reference plane is optic cup.

A topographic map of the optic nerve head is generated using a software algorithm (Fig. 1). Stereometric analysis provides a set of parameters useful for diagnosis of glaucoma and for monitoring of disease progression. These include disc area, cup-to-disc ratio, cup shape, height variation contour, rim area, rim volume, maximum cup depth, cup area, cup volume, RNFL cross-section area and mean RNFL thickness.

Reproducibility

Good reproducibility has been shown in normals, glaucomatous subjects and glaucoma suspects with coefficients of variation ranging from 2.9% to 6.4%.[14,15] Improved measurement reproducibility is achieved when a series of 3 examinations are obtained instead of a single image analysis.[16] Therefore, it is recommended that 3 images are obtained and averaged to create a mean topographic image.

Clinical Correlation

Several studies have shown strong correlation between various optic disc measurements measured by HRT and functional measurements obtained using automated static perimetry.[6,17] Brigatti and Caprioli[6] showed statistical correlation between cup shape measure and achromatic visual field indices in patients with early to moderate glaucoma. Teesalu et al[18] found a strong correlation between cup shape measure and short-wavelength automated perimetry. Mistlberger et al[19] found that RNFL thickness measured with HRT correlated with mean deviation of automated static perimetry and was able to differentiate glaucomatous from non-glaucomatous eyes.

Sensitivity/Specificity

Stereometric parameters obtained was able to differentiate normal and glaucomatous subjects.[19,20] By combining several parameters obtained from the HRT, Wollstein et al reported a highest specificity of 96.3% and sensitivity of 84.3% to separate normal subjects and those patients with early glaucoma using the 99% prediction interval from the linear regression between the optic disc area and log of the neuroretinal rim area.[20] This analysis, known as the Moorfields regression analysis has been incorporated into the latest HRT II software (version 1.5.0) (Fig. 2).

Clinical Use

The HRT has potential clinical use in screening, diagnosis and detection of progression. Presence of an age-matched normative database and a software programme incorporating the Moorfields regression analysis allow differentiation of normal from abnormal optic nerve heads. A fast, non-contact, non-invasive method for screening is possible. HRT provides an additional parameter to aid the clinician in making the differentiating glaucoma from glaucoma suspect. HRT provides objective parameters for monitoring and longitudinal follow-up of patients, in addition to the other conventional parameters described above.

Limitations

The main limitations for the HRT are the need to establish a reference plane and the need for correct placement of the disc contour line. Any change in these two factors can influence many of the stereometric parameters. The current normative database is limited and is based on Caucasian eyes. An ethnicity based normative data may be required for it to be more useful for Asian eyes.

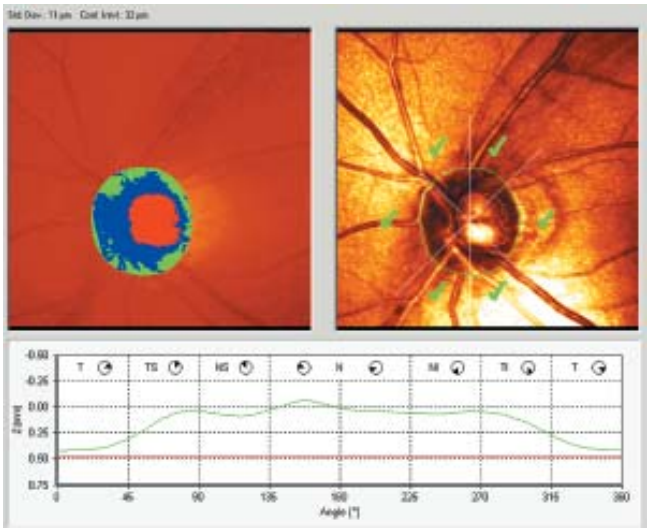

Fig. 1. Topographic map (left) and reflectance image (right) display of the confocal scanning laser ophthalmoscope. The regions coloured blue and green are above the reference plane and represent the neuroretinal rim. The red region is below the reference plane and represents the optic cup. The graphical display at the bottom displays the surface height variation along the contour line (optic disc margin).

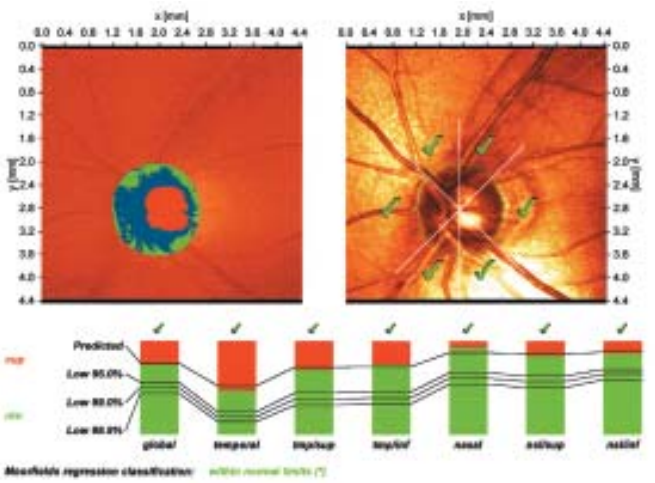

Fig. 2. Moorfields regression analysis in the HRT II (Heidelberg Engineering, Heidelberg, Germany). The ratio of the neuroretinal rim area (green and blue) to the optic disc area (green, blue and red) in the sector is compared to a normal database; the sector is then classified as within normal limits (green check mark), borderline (yellow exclamation mark) or outside normal limits (red cross). The exclamation mark and red cross are not shown in this figure.

Scanning Laser Polarimetry

Scanning laser polarimetry (SLP) is a noninvasive method for objective evaluation of peripapillary retinal nerve fiber layer (RNFL) thickness by utilising the birefringent properties of retinal ganglion cell axons. The parallel

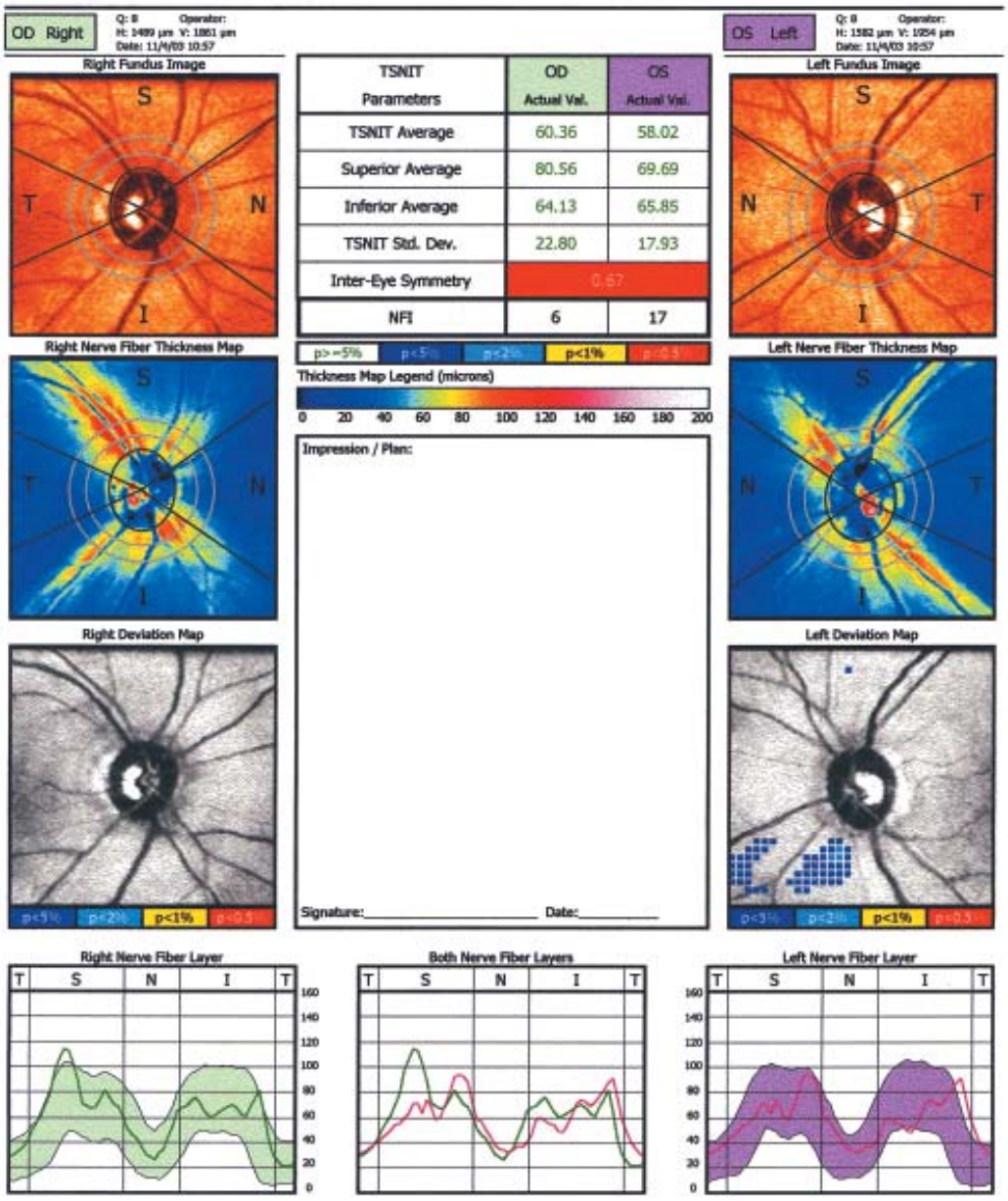

Fig. 3. Nerve fibre analysis of the right and left eyes with the GDx-VCC (Laser Diagnostic Technologies, Inc., San Diego, CA). The top image shows the fundus or reflectance image. The second image from the top shows the retardation map which is converted to a retinal nerve fibre layer (RNFL) thickness image. The RNFL thickness is colour coded based on the colour spectrum, with thinner regions displayed in blue and green and thicker regions displayed in yellow and red. The third image from the top is the deviation map. The location and severity of the RNFL loss are shown. Areas that fall below the normal range are colour coded according to the probability of normality. The graph at the bottom shows RNFL thickness measured along a measurement ellipse. The normal range is shown in the shaded area.

arrangement of microtubules within the nerve fibre provides linear birefringence. Essentially, the system consists of a confocal scanning laser ophthalmoscope with an integrated polarimeter. As polarised light from a diode laser light source (780 nm) passes the RNFL and is reflected back from the deeper layer, it undergoes a phase shift. This change, referred to as "retardation" is linearly correlated to the thickness of the polarizing medium, and is computed to give an index of RNFL thickness. A detection unit measures the retardation of light returning from the eye and calculates the RNFL thickness at each retinal location on a 256 x 256 pixel image. Retardation measurements correspond with known properties of the RNFL, with areas of increased retardation in the superior and inferior arcuate regions,

decreased retardation toward the periphery and overlying blood vessels, and decreased retardation with age.[21] Use of a near-infrared light beam (wavelength 780 nm) minimises reflectance from the retinal nerve fibers and absorption by the lens

An anterior segment compensating device has been incorporated into the machine to compensate for the polarization effects of other ocular birefringent structures such as the lens and cornea. The earlier versions of the instrument have a fixed system for compensation and assume a fixed slow axis of corneal birefringence 15 degrees nasally downward and a magnitude of 60 nm. Recent studies have shown that the magnitude and axis of corneal compensation are variable for different subjects.[22,23] This has prompted a change towards using a system with a variable corneal compensating device. This newer system has been renamed the GDx-VCC (Laser Diagnostic Technologies, Inc., San Diego, CA).

The GDx provides a set of parameters which include RNFL thickness measurements, modulation measurements and ratio measurements (Fig. 3). There is also a neural network derived value (GDx Nerve Fiber Indicator, NFI) which gives an indication of likelihood of glaucoma. The manufacturer is currently improving its normative database to allow for cross-sectional comparison and diagnosis. With an improved database which is age and ethnicity specific, this technology can potentially be a fast and objective screening tool for glaucomatous patients.

Reproducibility

Good intraoperator measurement reproducibility with low coefficient of variation has been demonstrated with SLP measurements.[24,25] Hoh et al[24] described excellent intra-operator reproducibility and showed that inter-operator variability can be minimised by using a single measurement ellipse from the baseline image and exporting it to subsequent images.

Sensitivity and Specificity

In a study comparing the summary data of HRT, GDx and OCT, the sensitivity and specificity of GDx has been shown to range from 72 to 82% and 56 to 82%, respectively.[26] In a cross-sectional study comparing OCT and SLP, Hoh et al[10] showed that SLP measurements was capable of differentiating glaucomatous from non-glaucomatous eyes, however, considerable measurement overlap exist between the 2 groups. Later work by Greenfield et al[23] showed that correction for corneal polarisation axis has been shown to significantly improve the discriminating power of SLP for detection of mild to moderate glaucoma.

Limitations

The early versions of the instrument used fixed corneal compensator devices. Variability in corneal polarisation axis and magnitude may affect retardation measurements.[22,23] However, this has been addressed in the newer version of the machine. As an improvement to the earlier versions of the GDx, the GDx-VCC has a built-in variable corneal compensator to determine and correct for anterior segment birefringence, from both the cornea and lens. Spurious RNFL thickness measurements may be obtained with anterior and posterior segment pathology such as ocular surface disease, media opacification and extensive peripapillary atrophy.[27,28] Caution should be exercised when interpreting data in cases with previous keratorefractive surgery.[29]

Optical Coherence Tomography

Optical Coherence Tomography device which is available commercially is manufactured by (Zeiss Humphrey System, Dublin, CA). The early development of the prototype system was a result of collaborative work between scientists and clinicians at the New England Eye Center, Massachusetts Institute of Technology and Lincoln Laboratories.

Low coherence near-infrared light (850 nm) from a super-luminescent diode laser is transmitted to the retina via a fibre optic delivery system. Backscatter from the retina is captured and resolved using a fiber-optic interferometer. Modulating the reference mirror allows longitudinal data to be extracted. Cross-sectional OCT images of the retina are constructed from the backscattering information provided by 100 individual axial A-scans. A digitised, composite image of the 100 A-scans is produced on a monitor with a false color scale representing the degree of light backscattering from tissues at different depths within the retina. Images are corrected for movement artifacts during scan acquisition using an image processing technique of cross correlation scan registration. A newer version developed by Zeiss-Humphrey Systems allows scanning with up to 512 A-scans within a similar duration of scan time of approximately 1 second.

Patients with a minimum pupillary diameter of 5 mm are required in order to obtain satisfactory OCT image quality. Images may be acquired using either a linear or circular scanning beam. Scanning acquisition time is approximately 1 second. A circular scan of the RNFL is generally performed with a diameter of 3.4 mm in order to avoid areas of peripapillary atrophy (Fig. 4). A computer algorithm identifies and demarcates the signal corresponding to the RNFL, and mean RNFL thickness measurements by quadrants and individual clock hours are calculated (Fig. 5). Normal RNFL thickness measurements are characterised by a "double-hump" appearance corresponding to the increased RNFL thickness along the superior and inferior poles of the optic nerve head.

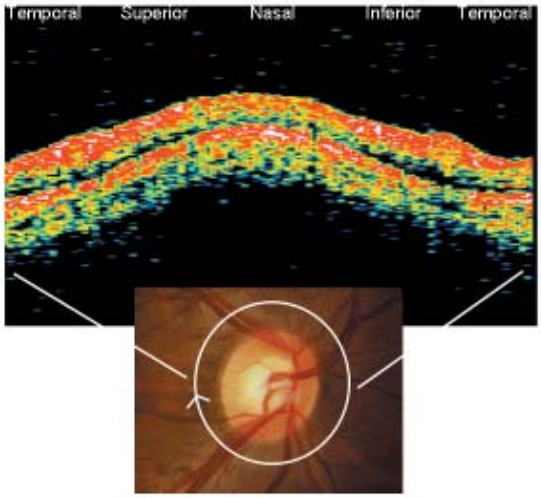

Fig. 4. Circular around the optic disc with optical coherence tomography (Zeiss Humphrey System, Dublin, CA). The image displayed corresponds with the circular scan starting temporally and moving superiorly, nasally and inferiorly and ending temporally.

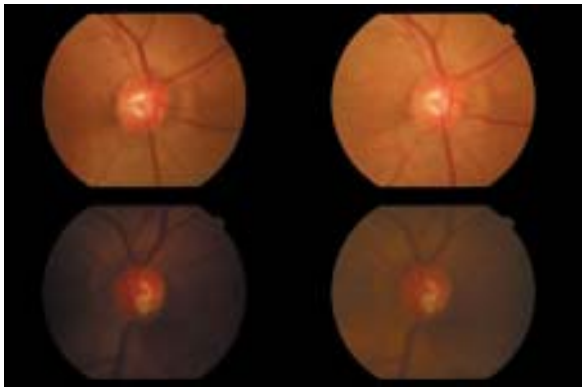

Fig. 6. Notching of left infero-temporal neuroretinal rim. A healthy neuroretinal rim was observed in the right.

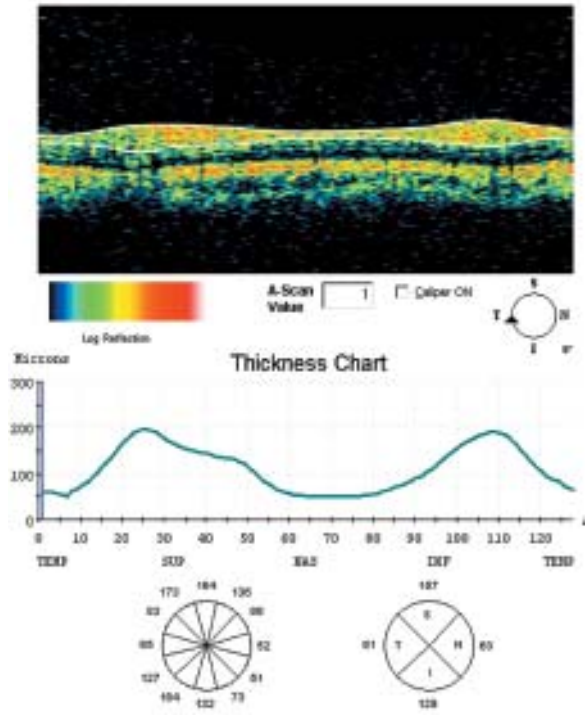

Fig. 5. Retinal nerve fibre layer (RNFL) thickness measured with a circular optical coherence tomography scan around the optic disc. A computer algorithm identifies and demarcates the signal corresponding to the RNFL. Mean RNFL thickness measurements by quadrants and individual clock hours are calculated and shown at the bottom of the figure. The RNFL thickness chart shows a typical "double hump" pattern in a normal eye, with thick RNFL in the superior and inferior quadrants.

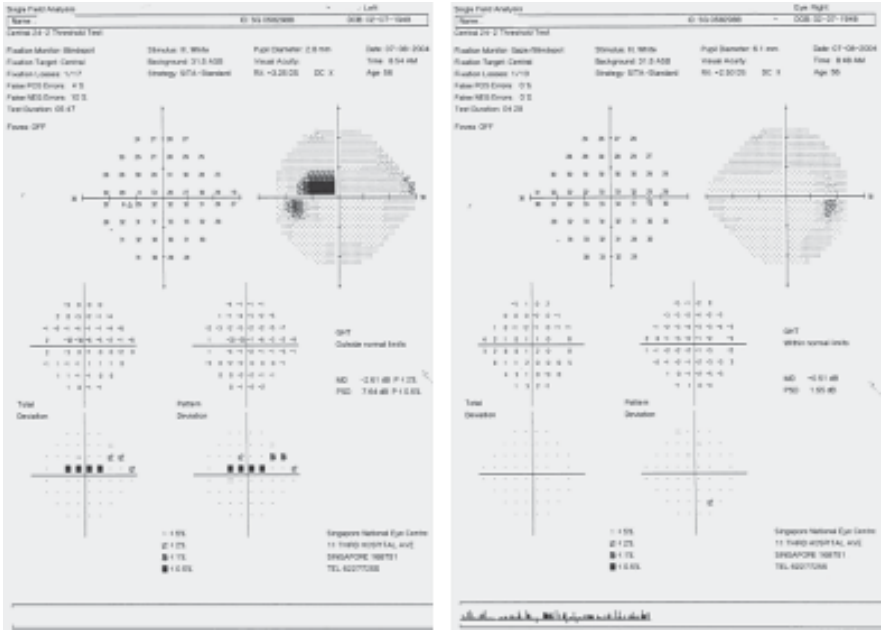

Fig. 7. Left superior paracentral scotoma on Humphrey 24-2 threshold visual field examination (MD -2.62, *P* <2%). Right visual field examination was within normal limits. (MD +0.51).

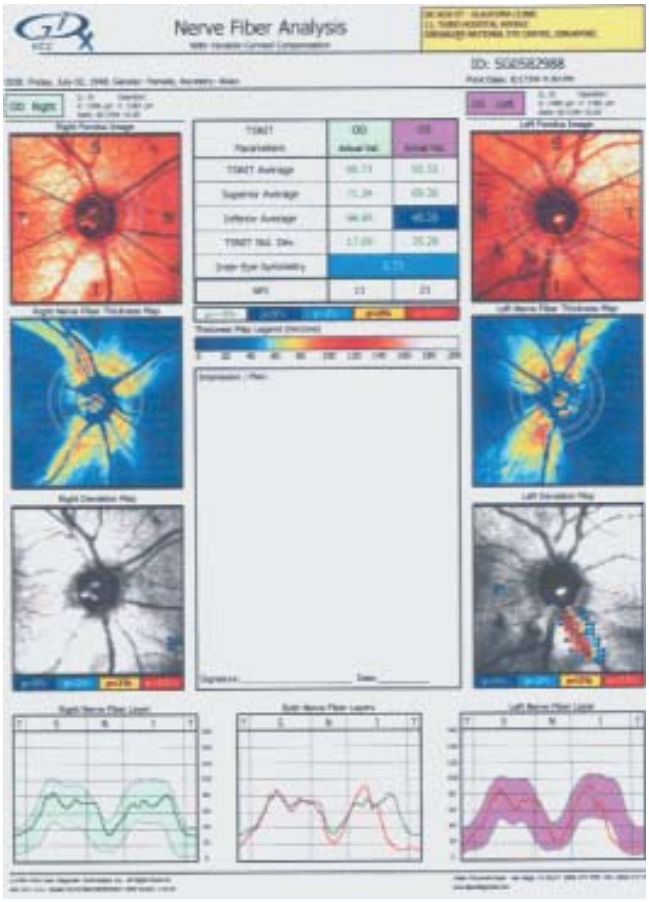

Fig. 8. Thinning of the RNFL, demonstrated on the deviation map of GDx-VCC scan which corresponded to the neuroretinal notching seen in the left eye.

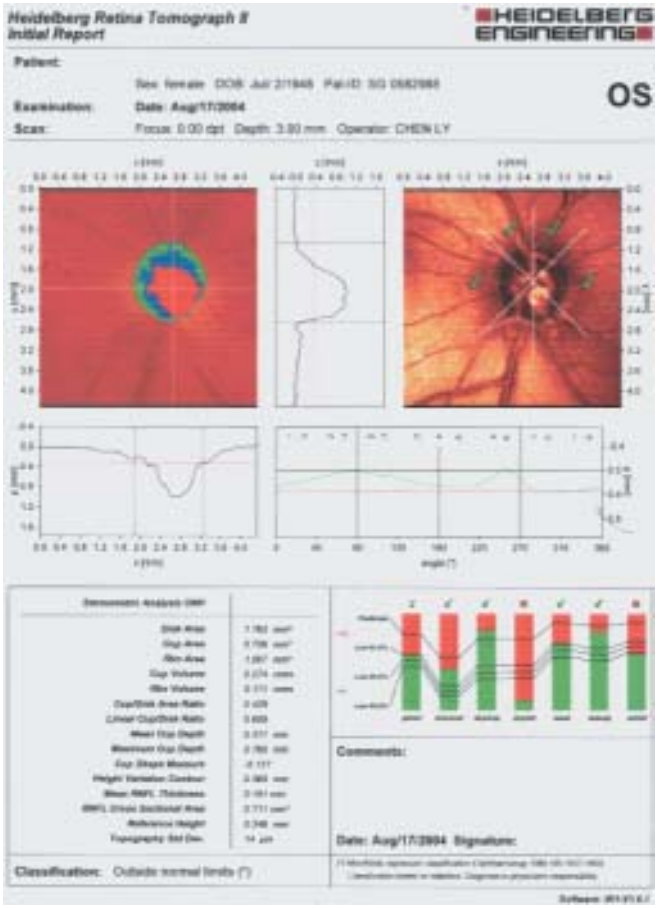

Fig. 9. Inferior neuroretinal rim thinning of the left optic nerve seen in a HRT II scan, as demonstrated in the topographic map (left). Red crosses in the reflectance image (right) showed abnormal rim area to optic disc area ratio.

Reproducibility

Several studies have reported good reproducibility for the OCT.[30,31] Schumann et al[30] compared measurements of RNFL thickness and retinal thickness using circular scan diameters of 2.9 mm, 3.4 mm and 4.5 mm. He also evaluated the use of internal fixation as compared with external fixation targets. He found that a circle diameter of 3.4 mm to be superior and that scans obtained with internal fixation targets were less variable compared with those obtained with external fixation targets. In a study by Gurses-Ozden et al, it was shown that a 4-fold increase in sampling density from 25 sampling points per quadrant to 100 sampling points per quadrant significantly improved measurement reproducibility in glaucomatous eyes.[32]

Sensitivity and specificity

In a cross-sectional study, comparing OCT with SLP in normal, ocular hypertensive and glaucomatous eyes, Hoh et al[10] found that OCT and SLP were capable of differentiating glaucomatous from non-glaucomatous eyes. However, considerable overlap was observed among normal, ocular hypertensive and glaucomatous eyes. Retinal nerve fibre layer thickness measurements obtained with OCT and SLP also demonstrated good correlation with visual field indices. Retinal nerve fibre layer thickness measurements obtained with OCT also demonstrated significant correlation with topographic measurements using CSLO.[19] The sensitivity and specificity of the OCT has been reported to range from 76% to 79% and 68% to 81% respectively.[26]

Limitation

The earlier versions of the OCT were limited by the number of sampling points which is 100 points per scan and speed of scanning. This has however been addressed in the later versions of the instrument which saw an increase of sampling points to 512 points per scan within an almost similar scan duration. Pupillary dilatation is required for a satisfactory peripapillary circular scan. At the time of writing, the manufacturers were in the process of building an age and ethnicity specific normative database.

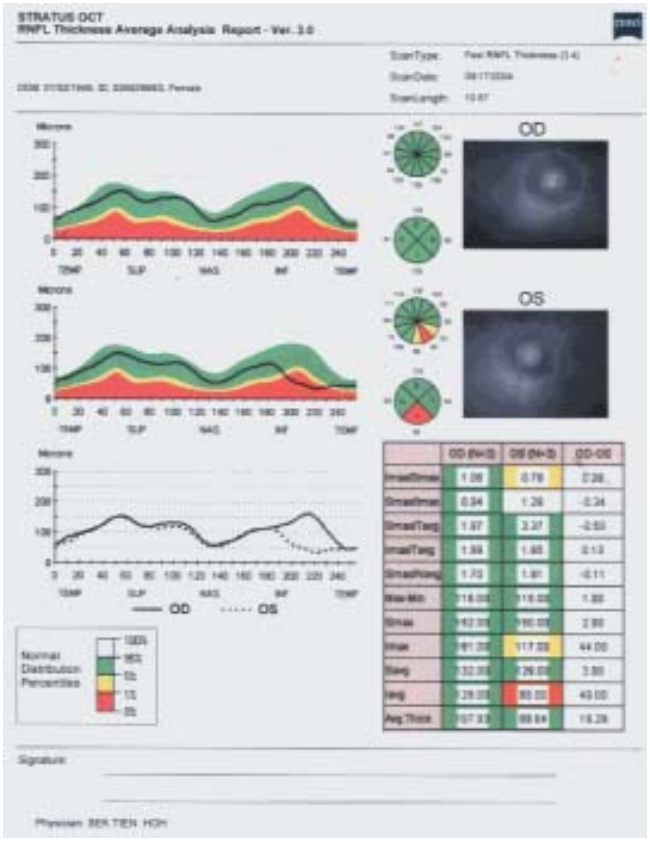

Fig. 10. Thinning of RNFL in the infero-temporal sector of the left optic nerve seen on an OCT scan. The RNFL thickness graph also showed loss of the "double-hump" pattern in the left eye when compared with the right.

Case Report

A 56-year-old Indian lady with pigmentary glaucoma. Visual acuity was 6/9 in both eyes. Intraocular pressure was 16 mm Hg in the right eye and 11 mm Hg in the left. She was on two anti-glaucoma medications for the left eye. Optic nerve examination revealed inferotemporal notching of the left neuroretinal rim and healthy looking right optic nerve (Fig. 6). Humphrey 24-2 threshold visual field examination revealed a left superior paracentral scotoma with a MD of -2.61 (P <2%) (Fig. 7). The right visual field was within normal limits with MD of +0.51. A GDx-VCC scan showed thinning of the RNFL which corresponded to the neuroretinal notching seen in the left eye, as demonstrated in the deviation map (Fig. 8). The HRT scan showed inferior neuroretinal rim thinning of the left optic nerve, as demonstrated in the topographic map and indicated by red crosses in the reflectance image (Fig. 9). Optical coherence tomography scan showed thinning of RNFL in the left infero-temporal sector of the optic nerve (Fig. 10). The RNFL thickness graph also showed loss of the "double-hump" pattern in the left eye as compared with the right.

The Role of Imaging

Developments over the past decade led to an explosion of imaging technologies for assessment of structural changes in the optic nerve and retinal nerve fibre layer. While questions arise regarding the actual benefit these instruments bring to the individual patient, the fact remains that these instruments have been shown to be accurate, objective, reproducible, non-invasive and fast. Sensitivity and specificity values fall in the range of 70% to 80%. There is tremendous potential for use of these technologies in screening, diagnosis and monitoring of glaucomatous patients. With increasing evidence for pre-perimetric changes in the optic nerve and RNFL before the onset of visual field changes, these instruments may be useful adjuncts to our current established methods of clinical examination, disc photography and perimetry. An on-going push towards improved normative databases that are both age- and ethnicity-based will make these technologies more effective as diagnostic and screening tools. In the meantime, quantitative measurements obtained by these machines provide useful parameters for monitoring of patients.

Conclusion

An effective and rapid screening tool for glaucoma, a leading cause of blindness, would benefit communities not only in developed countries but also in the less developed countries of Asia. Careful and prudent use of these imaging technologies in combination with telemedicine, may lighten the load and reduce the strain that is placed upon the public heath systems of poorer countries.

To date, there is no consensus on the best technology for assessing structural damage in glaucomatous optic neuropathy. Therefore, as with any investigation, clinical decisions should not be made on the basis of an isolated test. The clinician should exercise clinical correlation and judgment before instituting the appropriate treatment.

***Commercial interest**: The author has no proprietary interest in any of the products or techniques described in this manuscript.*

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