

HOW TO ASSESS THE RETINAL NERVE FIBER LAYER THICKNESS

Antonio FERRERAS

Miguel Servet University Hospital, Zaragoza. Aragón Health Sciences Institute University of Zaragoza (Spain)

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Primary open-angle glaucoma is a progressive multifactorial optic neuropathy characterized by an acquired loss of ganglion cells and their axons in the retina.^{1,2} Damage to the retinal nerve fiber layer (RNFL) is usually followed by changes in the optic nerve head shape and specific visual field defects. The recognition of defects in the RNFL is key for early glaucoma diagnosis.3,4 In glaucoma patients, the RNFL can be evaluated by red-free fundus photographs, scanning laser polarimetry (SLP), and optical coherence tomography (OCT). Monochromatic fundus photographs A series of red-free digital fundus photographs of each eye should be acquired for RNFL evaluation. One photograph must be centered on the optic disc and another two on each arcuate zone. The pattern of the fiber bundles can be detected as bright striations in the retinal reflex. In normal eyes, the RNFL is usually best visible in the inferior temporal part of the fundus, followed by the superior temporal region, the nasal superior region and the nasal inferior region.⁵ Different patterns can be observed in the assessment of RNFL by monochromatic fundus photographs (Fig. 1):

1) Slit-like RNFL defects are darker focal areas with reduced or lost visibility of the normal striation pattern; these are smaller than a first order branch vein, and do not extend to the disc margin. This pattern can be found in healthy eyes. 2) Wedge defects are darker focal areas with reduced or lost visibility of the normal striation pattern; these are wider than a first order branch vein, originating at the disk border and arching from the disc to the periphery. This is a typical

glaucomatous pattern. 3) Diffuse loss is a diffuse and generalized rarefaction of the normal striation pattern, which seems to blur into a uniform, dull, granular, white-gray area. The retinal vessels are normally embedded in the RNFL. In eyes with diffuse RNFL loss, the retinal vessels are covered only by the inner limiting membrane, resulting in better visibility and a sharper image of the large retinal vessels. This is also a finding of glaucomatous eyes, and requires an accurate inspection to be detected.

Red-free fundus photographs have been used for decades to qualitatively assess the RNFL status. The highly subjective nature of this method and the requirement for experienced evaluators, however, limit its general applicability.⁶ In recent years, different instruments have been introduced to quantitatively measure peripapillary RNFL thickness. New imaging devices that allow for quantitative analysis of RNFL thickness, such as SLP and OCT, provide a breakthrough for establishing a glaucoma diagnosis, and in some cases, for early





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Retinal nerve fiber layer redfree fundus photographs. (a): bright striations in the retinal reflex following an arcuate course around the fovea, in a normal individual. (b): slitllike RNFL defects can be seen in normal individuals. (c): Wedge defect in a glaucoma patient. (d): diffuse loss in a patient with advanced glaucoma.

glaucoma detection even before perimetric changes have been established.^{7,8}

Scanning laser polarimetry SLP is an imaging technology designed to provide objective assessment of the RNFL with potential use for diagnosis and follow-up of patients with glaucoma. It is based on the principle that polarized light doublepassing through the RNFL is split into two orthogonally polarized, phase shifted components. SLP measures the phase shift (retardation) of light that has passed the birefringent fibers of the RNFL. The amount of linear retardation of light at each corresponding retinal location is proportional to the RNFL thickness.9-11 Nevertheless, there are other birrefringent structures in the anterior pole (cornea and lens), which must be compensated. To neutralize the confounding influence of anterior pole birrefringent tissues on RNFL thickness, the polarimeter has an integrated variable corneal compensator (VCC), which determines and neutralizes eye-specific corneal polarization axis and magnitude using the concept of the macula as an intraocular polarimeter.¹²⁻¹⁴ The last version of SLP (GDx Pro, Carl Zeiss Meditec, Dublin, CA) includes the enhanced corneal compensation (ECC) software, which improves

compensation in atypical patterns of peripapillary birrefringent structure.^{15,16} To obtain reproducible measurements, scans must be of acceptable quality (well focused and centered with a quality report \geq 7). The GDx provides RNFL parameters based on a calculation circle, which is automatically placed around the optic disc. The calculation circle defines the area where data are acquired for the temporal-superior-nasal-inferiortemporal (TSNIT) parameters: TSNIT average, superior average, inferior average, TSNIT standard deviation, and inter-eye symmetry. The TSNIT parameters are color-coded according to a normative database indicating deviation from normality. Moreover, the GDx printout shows a learning classifier, the nerve fiber indicator (NFI), which is not a color-coded parameter. The NFI is calculated from a neural network analysis, trained to optimally discriminate between healthy and glaucomatous eyes. It analyses the RNFL profile and provides a single number representing the integrity of the entire RNFL. A higher number is more likely to be related to abnormality, but is not definitive (range from 1 to 100). It has been suggested the 95th percentile as the best cut-off point for glaucoma diagnosis (NFI value = 30). The GDx printout reports quality



fig. 2 Printout of the Cirrus optical coherence tomography (OCT, Carl Zeiss Meditec). The last version software for this OCT includes optic nerve head and retinal nerve fiber layer analysis in a single test.

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indicators, fundus images, nerve fiber layer maps, RNFL parameters, deviation maps, and RNF profiles compared with the normative database. The GDx also includes a software to evaluate progression, called Guided Progression Analysis (GPA), which compares an observed change with its expected test-retest variability. This analysis considers the two first examinations as baseline and then compares with it the follow-up tests. GPA uses the Image Progression Map to determine narrow focal defects, the TSNIT progression graph to find broader focal defects, and the Summary Parameter Chart to detect diffuse defects. Optical coherence tomography The first OCT imaging studies of the human retina were reported in 1993.^{17,18} Since then, this technique has been rapidly adopted into clinical practice and is now one of the main diagnostic methods in ophthalmology. The OCT employs the principles of low-coherence interferometry. It is analogous to ultrasound B-mode imaging, but it uses light instead of sound to acquire high-resolution images. The performance of OCT

has been constantly improved since its introduction and the latest generation, spectral-domain OCT, provides three-dimensional images having higher axial resolution compared to the previous OCT version, time-domain OCT (400 A-scan per second). Increased scanning speed (more than 20,000 A-scan/s) allows spectral-domain OCT to obtain a three dimensional cube of data, and advances in light source technology have enhanced axial resolution significantly. The cube of data enables a far more extensive assessment of the peripapillary area including TSNIT RNFL profiles, en face RNFL images (fundus image) and optic nerve head assessment (Figure 2). OCT is the only non-invasive method that enables physicians to obtain in vivo high-resolution crosssectional images of the retina. The fastest commercially available spectral-domain OCTs are Cirrus OCT (Carl Zeiss Meditec; 27,000 A-scan per second) and Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany; 40,000 A-scan per second). Both devices provide true RNFL thickness (in microns) at 6 or 12



sectors around the optic disc and an average RNFL thickness. All these thicknesses are color-coded according to a normative database. Cirrus OCT also includes the GPA software, which uses multiple algorithms to detect progression. The GPA printout shows from 3 to 8 RNFL thickness maps chronologically from left to right. The two first examinations are considered as baseline exam. Then, the follow-up scans (3rd through last) are compared to baseline exam and areas of statistically significant change are highlighted in yellow or red (focal change). Furthermore, the GPA evaluates RNFL thickness graphs to identify global thinning in the RNFL by calculating a trend over time (diffuse change). Spectral-domain OCT provides many potential advantages for glaucoma

diagnosis and follow-up. Axial resolution of commercially available units is currently close to 5 µm, and research systems are approaching 2 to 3 µm, which could lead to the detection of subtle changes in the RNFL and the optic disc and result in a better ability to detect disease progression. Moreover, the higher scan acquisition speed reduces artifacts and might help to obtain more accurate measurements, which also contributes to reduced measurement variability. Imaging technologies have some limitations. Quality of scans and the location of scan circle affects accuracy of the measurements,^{19,20} these instruments yield worse diagnostic ability in small and large optic discs,^{21,22} and there is not general agreement regarding the optimum criteria for glaucoma diagnosis and follow-up. Nowadays,

there is no a single imaging instrument that outperforms the others in differentiating patients with glaucoma from healthy individuals.

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