Assessment of retinal nerve fibre layer in primary open angle glaucoma

Essay

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Introduction

Glaucoma is a disease that is identified biologically by the death of retinal ganglion cells. The axons of these cells make up the retinal nerve fibres that gather at the optic nerve head and form the anterior-most layer of the retina .As retinal ganglion cells are lost, through processes not yet fully understood, the retinal nerve fibres are also lost, and this layer thins [(1)].

Patients at risk for glaucoma may have optic nerves and visual fields of normal appearance, but they may still have nerve fiber layer defects that are indicative of early, undetected glaucomatous damage [(2)]. If not diagnosed in early stage,the damage of the optic nerve and other structures becomes permanent, which in the final stage may leads to blindness. One of the glaucoma signs is the gradual loss of the retinal nerve fibers (RNF), which has been proved of high diagnostic value. The RNF atrophy is indicated as a texture changes in colour or greyscale retinal photographs.[3]

The introduction of modern imaging devices such as the confocal scanning laser ophthalmoscope, scanning laser polarimetry, and optical coherence tomography have offered objective and reproducible measurements of the topographic parameters of the optic nerve head(ONH) and nerve fibre layer(NFL).The scanning laser polarimeter (GDx Nerve Fiber Analyzer) was designed primarily to measure the NFL thickness around the optic disc, meanwhile the confocal scanning laser ophthalmoscopy (Heidelberg Retinal Tomograph) and optical coherence tomograph provide quantitative data of both NFL thickness

and topographic parameters of the ONH such as neuroretinal rim area and volume, cup-to-disc area ratio, and cup volume.[4]

Clinical Examination of the Retinal Nerve Fibre Layer(RNFL)

The importance of RNFL defects was first reported in 1973 by Hoyt et al. Evaluation of the RNFL is another useful tool to aid in the early diagnosis ofglaucoma. This is because nerve fiber layer defects can occur before disc changes and visual field changes are documentedor found.Thus ,RNFL loss could be theearliest sign of glaucoma.[5,6]

The current standard for evaluating the RNFLduring a dilated fundus examination consists of aninverted, stereoscopic image obtained with the slitlamp biomicroscope and a hand-held auxiliary lens.Commonly used lenses include the bi-convex, noncontact 60, 78, or 90 diopter hand-held lenses. Aslightly improved view can be obtained through acontact type lens, but this entails longer examination time, discomfort to the patient, and some temporary clouding of the cornea, which underminesthe view for subsequent photography or imaging.While simple and accessible, slit-lamp biomicroscopyof the RNFL is difficult to interpret, the data cannotbe quantified, and, just as important, a hard copy isnot generated. Focal wedge-shaped defects infrequently occur in glaucoma; however, they are easierto detect. In contrast, diffuse RNFL loss occurs morecommonly, but it is rather difficult to ascertain withconfidence.[7]

White light originating from the slit-lamp and reflected back by the RNFL is far from ideal for assessing the RNFL. While the longer wavelengths (red)readily penetrate the RNFL, the shorter ones (blue)are more readily reflected back, enabling detectionof RNFL loss. Paradoxically, the human eye is poorlysensitive to blue wavelengths, drastically limiting ourability to view the RNFL via a cobalt blue filter. A reasonable compromise between white and blue light isusing the green (red-free) filter, which is readilyavailable for any slit-lamp. However, the superiorityof photographic film in capturing the fine details ofthe RNFL reflectance image is clearly better thanwhat an observer's eye alone can visualize (even withred-free illumination) during a clinical examination.It would be safe to say that a well-exposed funduscolor photograph allows RNFL details to be betterscrutinized than does any type of real-time fundus examination, even under excellent conditions (e.g.,lighting, magnification and lens choice). This is incontrast to the situation with other retinal conditions(such as macular holes or peripheral retinal lesions),in which a photographic image often is no substitute for a thorough dynamic examination.[8]

STEREOSCOPIC FUNDUS COLOR PHOTOGRAPHS

Stereoscopic photographs provide a hard copysnapshot of the RNFL with improved resolution overa real-time slit-lamp examination. Still, many factorsundermine this technique. Often, small undilatablepupils, media opacity, or a lightly pigmented funduscan drastically compromise the

ability to observeRNFL details. More so, differences in exposure(lighting, film processing, etc.) and slight changes incamera angle may introduce variability that limitsthe ability of this technique to ascertain progression.

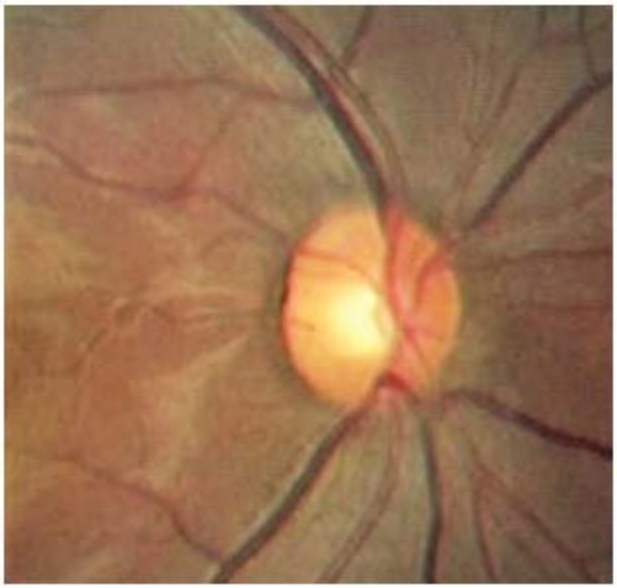

Fig. 1:normal glistening appearance ofRNFL[9]

RED-FREE MONOCHROMATIC RNFL PHOTOGRAPHS:

The same principles discussed regarding choice ofilluminating light wavelength for dilated clinical examinations holds true also for photography. The shorter(blue and green) wavelengths are morereadily reflected back from the RNFL, hence, contain more RNFL

information. Good quality RNFL red-free photographs are difficult to obtain, more so than color stereophotographs. However, when obtained, red-freephotographs better highlight the brightness and texture of the RNFL, as well as the degree to which thesmall retinal vessels are covered by RNFL (an indirect indication of RNFL thickness).[10]

One piece of evidence in favor of the use of red-free photographs is a study by Sommer et al[6] inwhich over 1300 ocular hypertensives were followedover a 6-year time period. Of the eyes that converted to glaucoma based on appearance of visual field defects, 50% and 85% (depending on the grader) hadRNFL defects as evidenced on red-free photographsat the time of field loss. In 60% of these cases, defects were present 6 years before the appearance ofvisual field loss.

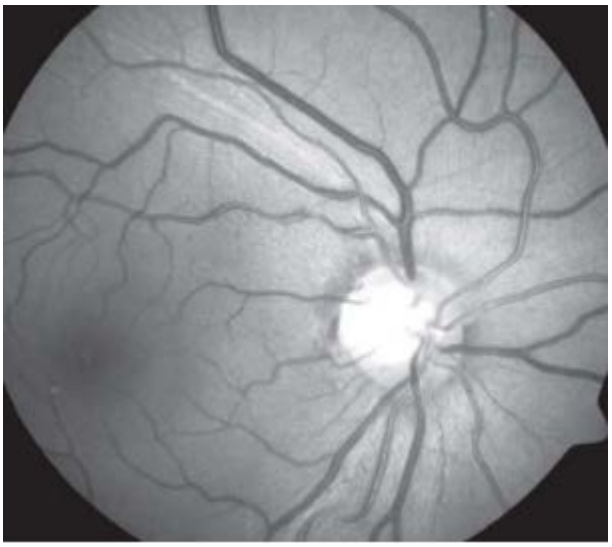

Fig.2: Normal appearance of RNFL in red-free photograph[9]

Patterns of RNFL loss:

Experimental studies have shown thatthe defects can be picked if 50% or more of the RNFL is lost. The firstglaucomatous axons to be lost are from the temporalraphe . Followingtypes of NFL defects may be seen:[5,6,11]

1.Slit defects: Dark areas which are slightly larger than arterioles and reach the disc following the normal course of the RNFL are called slit defects. They representretrograde degeneration of the axons due to focal damageot the optic nerve at the lamina.These can occur inapproximately 10% of normal patients. Slit like defect are difficultto identify and may be confused with the normal healthygrooves seen in normal RNFL

2. Wedge defects: caused by atrophy of manyganglion cells in the same area of the optic nerve. These defects start at the disc as narrow lines and expand as they get further from the disc. Notching of the neural rim tissue, as well as avisual field defect are often associated with wedge defects

Wedge shaped defect are usually seen in superior and inferiorpoles. They are easily detectable as compared to slit defectsand may be preceded by appearance of a splinter hemorrhagein the same site

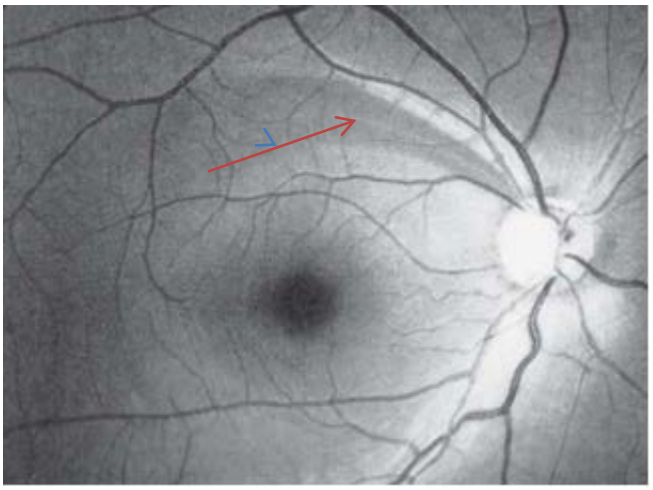

Fig.3: Red arrow:Wedge shaped defect[9]

3.Diffuse loss : is the commonest type of RNFL lossseen in glaucoma, but is difficult to pick up. The diffuse atrophytypically occurs in the superior and inferior arcades. The RNFL in these areas loses its consistency and looks like it has been combed or raked with darker and lighter areas.(fig. 4)

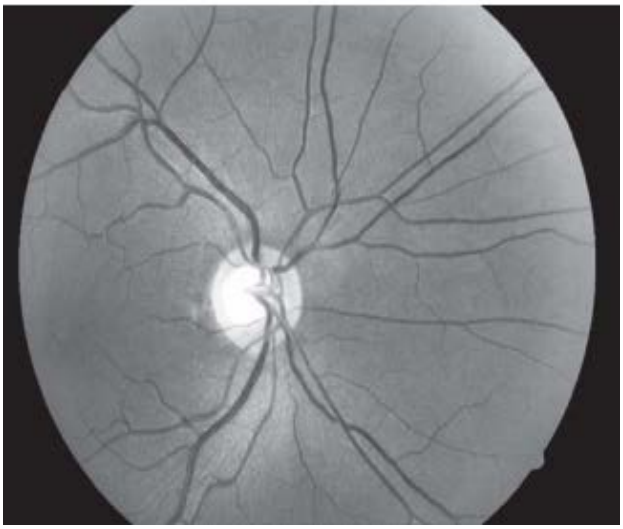

Fig. 4:diffuse RNFL loss[9]

4.Acombination oflocalizedanddiffuse loss RNFL defects are best seen within two disc diameters of the disc. When the NFL is thinned out, the blood vesselwalls are sharp and the vessel appear to stand out in reliefagainst a matt background. The initial abnormality in glaucomamay be either diffuse thinning or localized defects. Since theprevalence of true RNFL defects is <3% in the normal populationtheir presence is very likely to be pathological.

We should emphasize that non-glaucomatous RNFL defect is a common pathological change, which can be detected in a lot of systemic diseases such as hypertension, diabetes, and some CNS diseases including NAION, diseases that cause chiasmal compression, multiple sclerosis, Parkinson's disease and Alzheimer diseas.[12]

Distinguishing glaucomatous and other kinds of RNFL defect is crucial, especially in those eyes with normal intraocular pressure. This may provide ophthalmologists with some clinical clue for diagnosing as well as treatment protocol selection.First, we need to pay attention to the optic disc appearance. Usually, glaucomatous RNFL defect comes along with glaucomatous optic disc changes, as follows: (1) aabnormal vertical cup-to-disc ratio of the ONH ; (2) neuroretinal rim notching, thinning, or excavation; (3) an interocular difference in vertical cup-to-disc ratio 0.2.[13]

Secondly, the location of the RNFL defect would provide some new information. Studies have demonstrated that glaucomatous RNFL defect is mainly located at the inferotemporal (77.5%-92.3%), followed by the superotemporal meridian (54.2%).[14]Suh et al[15] reported previously that 92.3% of eyes with normal tension glaucoma (NTG), which had progressive RNFL defects, showed RNFL defects at the inferotemporal retina and 76.9% of eyes had RNFL defects only at the inferotemporal retina.

RNFL defect of patients with systemic diseases were located more in the superotemporal quadrants rather than the inferotemporal quadrant. Lee et al[13] investigated 40 patients with an unchanged RNF defect and normal optic appearance for more than 5 years. They found that the inferotemporal RNFL defects were presented in only 22.5% of the 40 eyes, they were mainly located at the superotemporal retina (77.5%).

Optical Coherence Tomography

Optical coherence tomography (OCT) is a rapid noncontact method that allows in vivo imaging of the retina, optic nerve head(ONH) and retinal nerve fiber layer (RNFL). In glaucoma, the OCT represents one of the methods capable of documenting and analyzing ONH and RNFL morphology in attempt to diagnose and monitor glaucomatous optic neuropathy.[16]

It is the optical analogue of ultrasound imaging. It provides high-resolution cross-sectional images of the retina, ONH and RNFL thickness that can be qualitatively and quantitatively evaluated. The OCT was first reported in 1991and since then, this technology has been evolving quite rapidly. Early models (OCT1 and OCT2, Carl Zeiss Meditec, Dublin, CA, USA) produced axial resolution at 12–15µm. The Stratus OCT model (Carl Zeiss Meditec, Dublin, CA, USA) is the latest commercial model of the conventional time domain OCT (TD-OCT), which scans four times more rapidly and is able to provide images with a theoretical axial resolution of approximately 10 µm.[17]

The spectral domain or Fourier domain OCT is a more recent commercial OCT model and uses a spectrometer as detector of OCT signal.It produces an axial resolution of 5µm.[18]

TIME DOMAIN OCT (TD-OCT)

The OCT contains a fibre optic Michelson interferometer that resolves the retinal structures by measuring the delay time of the light reflected and backscattered from different layers in the retina.TD-OCT (OCT version 1, 2, and Stratus OCT) compares the delay time of light reflected from the retina with the delay time

of the same beam reflected from a reference mirror at known distances. Interference occurs when the TD-OCT interferometer combines the reflected light from the retina with the reflected light from the reference mirror. A photo-detector detects and measures this interference using low coherence interferometry.[16]

Although the light reflected from the retina consists of multiple echoes (A-scans), the distance travelled by various echoes is determined by varying the distance to the reference mirror.(by moving the reference mirror closer and further from the beam splitter) Thus, the delay information is used to determine the longitudinal location of the reflection sites. This produces a range of time delays of the reference light for comparison. The light source is then moved across the retina, providing a two-dimensional map of reflections sites from the retinal microstructure. Digital processing aligns the A-scans to correct for eye motion, and digital smoothing techniques are used to further improve signal-to-noise ratio.[17]The OCT software locates the inner retina at the vitreo-retinal interface and the outer retina at the retinal pigment epithelial (RPE)-photoreceptor outer segment (OS) interface. These boundaries are determined based on differences in the image reflectance patterns.This techniqueallows Stratus OCT to acquire 512 A-scans in 1.3 sec, which may lead to some limitations in image acquisition of non-adjacent areas of the retina because of subtle eye movement during the scanning process, and preclude a more dense sampling of the evaluated area.[19]

SPECTRAL DOMAIN OCT (SD-OCT)

Recently, Fourier domain OCT (or spectral domain OCT) has become available, enabling considerable improvements in image acquisition speed and image resolution. In SD-OCT the reference

mirror is stationary, and the OCT signal is acquired by using a spectrometer as detector.[18]

Mathematically, Fourier transforms are used to extract the depth information. These characteristics permitted SD-OCT to increase the image acquisition speed up to 18 000-55 000 A-scans per second, reducing the vulnerability to involuntary eye movement artifacts, and permitting a denser sampling of the tissue.[20] High-resolution three-dimensional (3D) reconstructions have become feasible, and may be useful in better defining the topography of the optic disc, thickness of the RNFL and potentially other layers of the retina, such as the retinal ganglion cell layer.[21]

Whereas several commercial spectral domain OCT devices are currently available from several different manufacturers (Table 1), it is currently unclear which device will prove superior in clinical practice and research settings. In addition to enabling 3D mapping of the retina and optic disc, the improved resolution in imaging retinal layers now allows for reliable visualization of tissue layers in most subjects not possible with the previous technology, including the photoreceptor outer segment and ganglion cell layer.[22]