

Advances for Early Diagnosis of Primary Open Angle Glaucoma

An Essay submitted for partial fulfillment of Master Degree
of Ophthalmology

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LIST OF ABBREVIATIONS

ARPs	Atypical Retardation Patterns
Asb	Apostilb
AUC	Area Under Curve
BL	Border Line
CA	Cup Area
CI	Confidence Interval
CpRNFL	Circumpapillary Retinal Nerve Fiber Layer
CPSD	Corrected Pattern Standard Deviation
CSLO	Confocal Scanning Laser Ophthalmoscopy
CV	Cup Volume
dB	Decibel
FDT	Frequency doubling technology
FE	Fellow Eye
FL	Fixation losses
FNs	False Negatives
FPs	False Positives
GDx ECC	Enhanced Corneal Compensation
GDxFCC	Fixed Corneal Compensator
GDxVCC	Variable Corneal Compensation
GHT	Glaucoma Hemifield Test
GPA	Guided Progression Analysis
GPS	Glaucoma Probability Score
HFA	Humphrey Field Analyzer
HM	High Myopia
HRT	Heidelberg Retina Tomograph
IOP	Intraocular Pressure
IPL	Inner Plexiform Layer
MD	Mean Deviation
MGCC	Macular Ganglion Cell Complex
MRA	Moorfields Regression Analysis
My cells	Magnocellular Ganglion Cells
NFI	Nerve Fiber Index
NRA	Neuroretinal Rim Area
NTG	Normal Tension Glaucoma

OCT	Optical Coherence Tomography
ODA	Optic Disc Area
OHT	Ocular Hyper Tension
ONH	Optic Nerve Head
ONL	Outside Normal Limits
P	Probability Values
PCO	Posterior Capsular Opacification
POAG	Primary Open Angle Glaucoma
PPG	Preperimetric Glaucoma
PSD	Pattern Standard Deviation
Py cells	Paravocellular Cells
RNFL	Retinal Nerve Fiber Layer
RPE	Retinal Pigmented Epithelium
SAP	Standard Automated Perimetry
SD	Standard Deviation
SD-OCT	Spectral Domain OCT
SF	Short-Term Fluctuation
SITA	Swedish Interactive Threshold Algorithm
SLP	Scanning laser polarimetry
SN	Signal-to-Noise Ratio
SVM	Support Vector Machine
SWAP	Short-Wavelength Automated Perimetry
TDOCT	Time Domain-OCT
TSNIT	Temporal–Superior–Nasal–Inferior–Temporal
TSS	Typical Scan Score
WNL	Within Normal Limits

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Introduction

Glaucoma is characterized by progressive degeneration of retinal ganglion cells and their axons that leads to nerve fiber layer loss, optic disc cupping and consecutive glaucomatous visual field changes. (1)

Early glaucoma detection is crucial for the prognosis of the disease and treatment by preventing the progression of irreversible restriction of the visual field. (2)

Standard automated white-on-white perimetry (SAP), frequency-doubling technology (FDT) perimetry, and short wavelength automated perimetry (SWAP) are three of the prevailing visual field testing technologies in use in clinical practice. Although SAP is considered the reference standard for detecting visual field loss in glaucoma, there is evidence suggesting that FDT perimetry and SWAP detect visual field changes earlier than SAP does. (3)

Combination of FDT and OCT seem to be useful for detecting possible preperimetric glaucoma (both structural and functional abnormalities) in disc suspects and OHT eyes, and may be useful tools for identifying those individuals who warrant close follow-up for detecting glaucoma by SAP. (4)

The deterioration of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) often precede the visual field loss detected by perimetry. Imaging technologies for evaluation

of the ONH and RNFL are useful in the differentiation between glaucomatous and normal eyes. (5)

Computer-based devices such as confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography provide quantitative assessments of structural damage to ONH and RNFL. (6)

Confocal Scanning Laser Ophthalmoscopy (CSLO) is used to evaluate topographic changes in the ONH and in neuroretinal rim area (RA) in glaucoma patients . (5)

The latest generation of CSLO is the Heidelberg retina tomograph III (HRT III) that provides numerous stereometric parameters, including disc area, rim area, and cup area that assist clinicians in assessing the anatomical features of the optic disc. (7)

Classification indices such as the Moorfields regression analysis (MRA) and the glaucoma probability score (GPS) which highlight regions as “outside normal limits” are among the HRT tools currently used to discriminate between healthy and glaucomatous discs.(7)

Scanning Laser Polarimetry (SLP) measures RNFL thickness. The available SLP instruments are the GDx VCC (variable cornea compensation) and the latest GDx ECC (enhanced corneal compensation). The GDx has been shown to discriminate well between glaucomatous and healthy eyes in earlier stages of disease . (7)

Optical coherence tomography (OCT) provides high resolution cross-sectional images of the RNFL and ONH that

give accurate and objective anatomic diagnosis of glaucoma . several SDOCT devices as the RTVue, the Spectralis OCT, the 3D OCT can discriminate between healthy eyes and those with perimetric glaucoma . (8,7)

Finally, Interpretation of instrument results for detection of glaucoma and monitoring its progression remains a challenge . (7)

Aim of this essay

To review the advances in early diagnosis of open angle glaucoma .

PRIMARY OPEN ANGLE GLAUCOMA

Primary open angle glaucoma (POAG) is still one of the major causes of blindness in the world. Glaucoma is defined clinically as progressive optic neuropathy characterized by cupping of the optic nerve head, focal or diffuse thinning of the retinal nerve fiber layer and subsequently followed by characteristic visual field loss.(1)

The main clinical features of POAG are an open iridocorneal angle and cupping of the optic nerve head (ONH) (or optic disc), with corresponding loss of visual field. It is also characterized by absence of signs of secondary glaucoma or a non glaucomatous cause for the optic neuropathy. Elevated intraocular pressure (IOP) is not part of the clinical definition because POAG can occur when IOP is normal (typically 10 to 21 mmHg). Nevertheless, elevated IOP is an important risk factor and is also considered to be a causative factor in glaucoma. (2)

Other risk factors are old age, race and positive family history. At the genetic level, a distinction between juvenile onset (age at diagnosis 10–35 years) and adult onset (age at diagnosis above 35 years) has been made. Many juvenile onset cases have autosomal dominant inheritance whilst adult onset cases are typically multi factorial. Other factors include increased

glutamate levels, alterations in nitric oxide (NO) metabolism, vascular alterations and oxidative damage caused by reactive oxygen species (ROS). (3,4)

It has been demonstrated that 20-40% of optic nerve axons can be lost before irreversible visual field defects are observed in standardized automated perimetry. Thus detection of optic nerve head and retinal nerve fiber layer (RNFL) damage is crucial for the diagnosis of glaucoma in its early stages.(5)

Evaluation of the relationship between anatomical structure (optic nerve and retinal nerve fiber layer [RNFL]) and function (visual sensitivity) in glaucoma can aid in assessing the relative efficacy of structural and functional tests in detecting glaucomatous damage and in their optimal use. Although a significant relationship is expected between structure and function because both provide related information, studies using the available measurement methods have shown that this relationship is modest at best. One reason for this imperfect relationship may be the variability associated with measurements obtained using currently available methods. (6)

White-on-white standard automated perimetry (SAP) has been most widely used for assessment and followup of functional damage in glaucomatous eyes. Its result is, however, known to be relatively insensitive to functional damage of retinal ganglion

cells (RGCs) in the early stage of glaucoma, although recent studies indicated that functional damage can also occur before structural damage. (7)

Frequency doubling technology (FDT) was developed based on a phenomenon first demonstrated by Kelley, the frequency doubling illusion, which occurs when a low spatial frequency (0.25 cycles per degree) sinusoidal grating undergoes rapid (25 Hz) counterphase flicker. (8)

Several studies have shown that FDT stimulus predominantly stimulates the M-cells representing about 10% of all RGCs with axons projecting into the magnocellular layer of the lateral geniculate nucleus, with partial contribution of input from other RGCs and cortical mechanism. In contrast to the first generation of FDT, the Matrix FDT perimeter increases the spatial resolution by adopting a 24-2 testing pattern similar to SAP.(9)

Short-Wavelength Automated Perimetry (SWAP) generates a blue-violet (440-nm wavelength) stimulus over a bright yellow background and may preferentially stimulate the RGCs in the koniocellular pathway. The Swedish Interactive Thresholding Algorithm (SITA) has been incorporated into SWAP to shorten test duration and improve test-retest variability. These