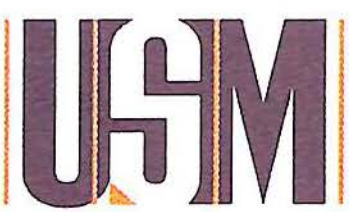
A STUDY ON THE CAPABILITY OF FREQUENCY DOUBLING PERIMETRY IN THE DETECTION OF VISUAL FIELD ABNORMALITIES IN PRIMARY OPEN ANGLE GLAUCOMA PATIENTS

By

DR NOR FADZILLAH ABD JALIL
(MD UKM)

Dissertation Submitted In Partial Fulfillment For The Degree Of Master Of Medicine (Ophthalmology)



UNIVERSITI SAINS MALAYSIA

SCHOOL OF MEDICAL SCIENCES
UNIVERSITI SAINS MALAYSIA
2007

DISCLAIMER

I hereby certify that the work in this dissertation is done on my own

Date: 7-12-2006

Nor Fadzillah Abd Jalil

PUM 1226

ACKNOWLEDGEMENT

I would like to express my thanks to my supervisor, Dr Bakiah Shaharuddin, lecturer of Department Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia, for her guidance and support throughout the duration of the study. My sincere gratitude to Dr Wan Hazzabah Wan Hitam, Head of Department of Ophthalmology who was formerly my supervisor for his guidance during the planning and preparation of the protocol.

A special thanks to Dr Kamarul Imran, from Department of Community Medicine, Dr Sarimah Abdullah and Dr Tg Norbanee Tg Hamzah from Department of Biostatistic and Methodology for their assistance in the statistical analysis.

My thanks to all lecturers in the Department of Ophthalmology, for their outstanding teaching, guidance and encouragement throughout the course. My warmest appreciation to all my fellow colleagues for their friendship, cooperation, assistance and encouragement.

To my children Nur Shahirah, Siti Aishah and Amirul Fikri, my utmost sorry for not always being around due to the busy schedule. To my beloved husband, Dr Mohd Azmi Abd Ghani thanks for your understanding, cooperation, encouragement and full support throughout the course.

My warmest appreciation to my parent and family in-law for their support and encouragement.

TABLE OF CONTENTS

PAGE

CHAPTER 4.0: RESULTS

PAGE

CHAPTER 8.0: APPENDICES

LIST OF TABLES:

PAGE

LIST OF FIGURES:

PAGE

ABSTRAK:

Pengenalan: Perimeter Frekuensi Gandadua "Frequency Doubling Perimetry" (FDP) telah digunakan secara meluas untuk tujuan saringan dan rawatan susulan medan penglihatan bagi pesakit glaukoma. Ianya dikatakan sensitif dalam mengesan kehilangan medan penglihatan akibat glaukoma kerana ia menguji sebahagian kecil populasi sel ganglion retina (sel M) yang merupakan 10% daripada keseluruhan sel retina. Maka dengan sebab itu ia dikatakan dapat mengesan kehilangan medan penglihatan lebih awal di kalangan pesakit glaukoma.

Objektif: Untuk menentukan keupayaan FDP di dalam mengesan ketidaknormalan medan penglihatan dikalangan pesakit glaukoma sudut terbuka, " Primary Open Angle Glaucoma" (POAG).

Bentuk Kajian: Prospektif, perbandingan dan kajian rentang.

Metodologi: Seramai 150 pesakit POAG telah menjalani ujian medan penglihatan menggunakan FDP bagi kedua-dua modul saringan dan tahap upaya (threshold) 30-2 dan mesin medan penglihatan Humphrey 30-2 di klinik mata Hospital Universiti Sains Malaysia (HUSM). Kesemua pesakit juga menjalani pemeriksaan oftalmologi termasuk ketajaman penglihatan, tekanan intraokular ukuran "cup-disc-ratio" (CDR) dan pemeriksaan sudut serambi hadapan (anterior chamber angle). Data yang diperolehi dianalisa menggunakan sistem SPSS versi 12.0 bagi mengetahui sensitiviti, spesifisiti, kawasan dibawah lengkungan "receiver operating characteristic" (ROC) dan ujian persetujuan diantara FDP dan "Humphrey visual field" (HVF).

Keputusan: Data 117 pesakit POAG telah dianalisa mengikut ciri - ciri inklusi dan eksklusi serta kebolehan gunapakai (reliability) ujian medan penglihatan. Untuk FDP dalam modul saringan, apabila "sekurang-kurangnya satu poin tercicir" digunakan sebagai definisi ketidaknormalan medan penglihatan, apabila dibandingkan dengan HVF sensitiviti yang diperolehi adalah diantara 92.2% hingga 96.2% dan spesifisiti di Antara 14.3% hingga 19.3%. Apabila "2 atau lebih poin" yang tercicir, dijadikan sebagai definisi untuk ketidaknormalan medan penglihatan, sensitiviti yang diperolehi adalah diantara 89.5% hingga 95% dan spesifisiti diantara 29.0% hingga 35.7%. Bagi FDP dalam modul tahap upaya dengan pelbagai definisi yang digunakan untuk ketidaknormalan medan penglihatan, sensitiviti yang diperolehi terletak diantara 83.5% hingga 100% dan spesifisiti pula berada di antara 0.0% hingga 50.0%. Nilai persetujuan kappa di antara FDP dan HVF didapati diantara 0.074 hingga 0.341 iaitu terletak diantara persetujuan yang "poor" hingga "slight".

Kesimpulan : Di dalam kajian ini, FDP menunjukkan sensitiviti yang tinggi tetapi spesifisiti yang rendah di dalam mengenalpasti ketidaknormalan medan penglihatan dikalangan pesakit POAG. Klasifikasi baru bagi keterukan glaukoma menggunakan 'Glaucoma Scoring System 2 (GSS2) dan 'Frequency Doubling Technology Scoring System 2' (FDT SS2) berupaya memberikan klasifikasi dengan segera dan boleh digunapakai untuk menentukan tahap keterukan glaukoma dan ciri-ciri ketidaknormalan medan penglihatan. Nilai persetujuan kappa diantara FDP dan HVF adalah diantara "poor" dan "slight".

ABSTRACT

Introduction: Frequency Doubling Perimetry (FDP) has become a more widely used technique for both screening for glaucoma patients and follow up of glaucomatous field loss. It is thought to be sensitive to glaucomatous visual field loss because it tests a sparse population of retinal ganglion cells (M cell) which comprise approximately 10% of entire retinal ganglion cells. Therefore it is superior in the detection of early visual field loss in glaucoma patients than other present conventional methods.

Objective: To determine the capability of FDP in the detection of visual field abnormalities in the primary open angle glaucoma (POAG) patients.

Design: Prospective, comparative, cross sectional study.

Method: A total number of 150 POAG patients underwent both FDP in screening and threshold mode 30-2 and Humphrey Visual Field (HVF) 30-2 tests in Eye clinic Hospital Universiti Sains Malaysia (HUSM). All patients had a comprehensive ophthalmology assessment including visual acuity, intraocular pressure, cup-disc-ratio measurement and anterior chamber angle assessment. Data analysis including sensitivity, specificity, area under the receiver operating characteristic (ROC) curve and kappa agreement between FDP and HVF was performed using SPSS system version 12.0.

Results: Data from 117 POAG patients were analyzed following inclusion, exclusion criteria and reliability of the visual field testing. For FDP in screening mode, when "at least 1 missed point" was used as the definition for abnormal FDP, the sensitivity was high between 92.2% to 96.2% and specificity was between 14.3%

to 19.3%. When " 2 or more missed points", was used as definition for abnormal visual field, the sensitivity was 89.5% to 95.0% and specificity between 29.0% to 35.7% was achieved. For FDP in threshold mode and HVF with various definitions for abnormal visual field, the sensitivity was between 83.5% to 100% and specificity between 0.0% to 50.0%. Kappa value for FDP and HVF was between 0.074 to 0.341 which showed poor to slight agreement.

Conclusion: In this study, FDP showed high sensitivity but low specificity in the detection of visual field abnormalities among POAG patients. The new classification for severity of glaucoma with Glaucoma Scoring System 2 (GSS2) and Frequency Doubling Technology Scoring System 2 (FDT SS2) was able to provide immediate and reliable classification for both severity and characteristic of VF defect. Kappa value of poor to slight agreement was obtained between FDP and HVF.

CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

1.1 GLAUCOMA

Glaucoma is a group of optic neuropathies characterized by progressive irreversible loss of retinal ganglion cells due to damage to the optic nerve head with the characteristic pattern of optic nerve and visual field damage. It is the second leading cause of blindness (Quigley, 1996), (Bourne et al, 2003) and it was estimated that 66.8 million people in the world have glaucoma and of these 6.7 million are bilaterally blind (Quigley, 1996).

The prevalence of blindness from glaucoma is about 100 per 100,000 among people 51 to 60 years old and five times as high in the 71 years or older age group. In our local context, the National Eye Survey in 1996 found that the prevalence of blindness in the country was 0.29% and glaucoma contributed to 1.8% of the causes of blindness and 1.8% as the cause of low vision (Zainal et al, 1996).

Glaucoma is difficult to diagnose and manage because in early stage it is essentially a symptomless disease and in some cases patient may have normal intraocular pressure (IOP). Identification of the individual with glaucoma before they develop symptomatic visual loss is critically important to prevent or slow the progression of damage. The diagnosis of glaucoma is difficult to make in a single visit. Combination of several tests including history, visual field (VF), IOP, gonioscopy, optic nerve head assessment and nerve fiber layer analysis are imperative to make the correct diagnosis. Sometimes, a patient is followed for years before a decision to treat is made. In addition, some of the

patients may present for the first time with extensive vision loss that should have been prevented long ago.

1.2 PRIMARY OPEN ANGLE GLAUCOMA (POAG)

Of all types of glaucoma, the open angle glaucoma remains the most common type of glaucoma worldwide, effecting approximately 1 in 100 of the general population over the age of 40 years. It affects both sexes equally. Worldwide, studies found that more than 3 million people are blind in both eyes from POAG and more than 2 million people will develop POAG each year.

The prevalence of POAG differs among different countries. The prevalence was 1.6% in patients aged 30 years and older and increased to 2.52% in people 40 years of age and older (Dandona, 2000).

In the Segoria study, the estimated prevalence in the Spanish population was 2.1% for POAG. The prevalence of POAG increased with age ($p<0.005$) and tended to be greater in man (2.4%) than woman (1.7%) (Alfons et al, 2004).

The prevalence of POAG was higher among Japanese population with 3.9% compared to in other population (Iwase et al, 2004). In Singapore, the population based study of Singaporean Chinese showed POAG to be a predominate form (49%) of all glaucoma (Foster et al, 2000). A population based survey in Rom Klao District, Bangkok showed that glaucoma was the second most common cause of severe unilateral visual loss and POAG accounted for 67% of all glaucoma (Bourne et al, 2003).

The prevalence of POAG may differ between races. From numerous large population studies, the proportionate prevalence of glaucoma among races indicated that race might play an important role as a risk factor in glaucoma. In the Blue Mountains Eye Study comprising of 3654 subjects, the prevalence of open angle glaucoma was 3.0% (Mitchell et al, 1996). Among Caucasians, POAG accounts for approximately 70% of their glaucoma patients (Quigley and Vitale, 1997).

Race was found to play a role in the prevalence of POAG. Some studies have found that the average IOP in blacks is higher than in whites, while other studies showed no difference (Wadhwa and Higginbotham, 2005). Some epidemiological studies noted glaucoma is the most common cause of blindness among people of African descent. They are more likely to develop glaucoma early in life and they tend to have a more aggressive form of the disease. Blacks are considered to have 3 to 4 time greater risk of developing POAG than whites. Blacks are also 6 times more likely to have optic nerve damage than whites.

Findings from the recent Ocular Hypertension treatment study suggested that blacks might have thinner corneal, which could cause their eye pressure to be measured erroneously low in the office. This may be a contributing factor to the large prevalence of severe glaucoma damage in African Americans at the time of diagnosis. More recent retrospective studies found that there was a statistically significant difference in the mean central corneal thickness between African Americans and the other ethnic group (Shimmyo et al, 2003).

However, in Asian population the incidence of Primary Angle Closure Glaucoma (PACG) is higher. Seah et al (1997) reported a higher incidence of PACG in Singaporean Chinese (12.2 per 100, 000 per year) compared to that of Singaporean Malays (6.0 per 100, 000 per year) and Indian (6.2 per 100, 000 per year). Similarly, Lai et al (2001) reported a high incidence of acute primary angle closure glaucoma among Hong Kong Chinese with incidence of 10.4 per 100, 000 per year.

Other important risk factors of glaucoma include increasing age and family history. The Barbados Eye Study (Leske et al, 2001) found that the incidence of open angle glaucoma was found to increase by approximately 2.5 times from 1.2% at age 40 to 49 to 4.2% at the age of 70 and above and is strongly associated with positive family history of open angle glaucoma. Some studies showed a higher prevalence of POAG among males (Leske et al, 2001, Wolfs et al, 2003), but other showed otherwise (Mitchell, 1996).

POAG is a multifactorial syndrome in which acquired progressive optic nerve damage is related, at least in part, to IOP higher than the nerve fibers can tolerate (Tarek et al, 2000). It is a group of chronic, bilateral conditions that are almost always symmetrical.

POAG is characterized (in at least one eye) by all the following features (AAO, 1996): evidence of glaucomatous optic nerve damage; adult onset; normal appearing open anterior chamber angle and absence of other known causes of open angle glaucoma. The characteristic of optic disc and retinal nerve fiber layer includes thinning or notching of neuroretinal rim, progressive increase in cupping of the optic nerve, acquired pit of the

optic nerve, retinal nerve fiber layer defects, and flame-shaped hemorrhage crossing the outer edge of the disc. The presence of damage of the visual field is evidenced by arcuate defect, nasal step, paracentral scotoma and generalized depression in the absence of other causes or explanation for the field defect.

The IOP is a definite and important risk factor for developing glaucomatous damage but is not sufficient for a diagnosis. The prevalence of POAG is higher with increasing IOP. IOP has a diurnal variation with normal individual varies 2-6 mm Hg over 24 hours period as aqueous production changes. There was 80% of patients peak between 8 to 12 in the morning. Any fluctuation greater than 10 mmHg is suggestive of glaucoma. The distribution of the IOP within the general population has a range of 11 to 21 mmHg (Johnson et al, 2000). Although there is no absolute cut-off point, 21 mmHg is considered upper limit of normal and levels above this are viewed with suspicion.

1.3 OPTIC DISC CHANGES

In glaucoma, the type of optic neuropathy has a characteristic increased in optic disc cupping and typically seen at later stages as an excavation of the optic disc on funduscopy examination. The neuroretinal rim, i.e the area containing the retinal nerve fibres, has different thickness at different region of optic disc.

In a normal disc with small cups the neuroretinal rim usually thickest (83% of eyes) in the infero-temporal sector followed by the supero-temporal, nasal and then temporal sector (I.S.N.T) rules (Jones et al, 1988). This pattern is less marked in a larger disc, in which the rim in distributed more evenly around the edge of the disc.

Glaucoma is characterized by progressive thinning of the neuroretinal rim. The pattern of tissue rim loss varies and may take the form of diffuse thinning, localized notching, or in combination. Thinning of the rim, while occurring in all disc sector, is generally greatest at the inferior and superior poles, leading to a loss of the physiological rim shape so that the inferotemporal rim is no longer the thickest (Zeyen et al, 1993). The optic cup often enlarges in a small direction, but usually the enlargement occurs predominantly in the vertical direction, as a result of rim loss at the poles.

Cup- to- disc ratio (CDR) is the decimal value obtained by dividing the cup diameter with the disc diameter. The closer the value means the damage is worse. The vertical CDR is a better measure of deviation from the normal than the horizontal ratio, because early neuroretinal rim loss occurs preferentially at the upper and lower poles of the disc. A difference in CDR between 2 eyes with equal overall optic disc size is suggestive of tissue loss and therefore is highly suspicious of acquired damage.

Although clinical examination still remains the most important method of assessing the optic nerve head for glaucomatous damage, several imaging devices are now available, allowing quantitative measurement of nerve structures and may aid clinical management (Mardin et al, 2001). These include confocal scanning laser ophtalmoscopy (e.g. Heidelberg Retina Tomograph (HRT)), scanning laser polarimetry (e.g. GDx), optical coherence tomography (OCT) and retinal thickness analyzer (RTA).

However, the process of categorizing patients by means of imaging device measurement is not the same as diagnosis. Diagnosis must also integrate all the other available

information about the patient, including clinical assessment of the optic nerve head and retinal nerve fiber layer, visual field and risk factors including IOP, age and family history.

1.4 VISUAL FIELD

Visual field testing is one of the routine and important components in glaucoma management. It is three-dimensional and has been described as an island of vision in a sea of darkness. It is not a flat plane but a three dimensional structure akin to a hill of vision. In a normal person, the VF limits are approximately 50 degrees nasally, 60 degrees superiorly, 70 degrees inferiorly and 90 degrees temporally. Visual acuity is sharpest at the very top of the hill (i.e. the fovea) and declines progressively towards the periphery, the nasal slope being sharper than the temporal. A visual field defect consist of an area of absolute or relative decreased in retinal sensitivity extending from an edge of the visual field.

Visual field measurement is a critical component in the armament against potentially blinding disease. The use in glaucoma is often discussed and well understood, however it has various other applications that render it useful in disease management and blindness prevention. Early visual field tests were based on kinetic stimulus presentation which response to a moving peripheral stimulus. During the test, patient looks straight at the stationary fixation point. A stimulus is moved from a non seeing area of the visual field to a seeing area along a set meridian. The procedure is repeated with the same stimulus along other meridians, usually spaced every 15 degrees. The luminance and size of the target is changed in order to plot areas of different light sensitivity. The

classic Tangent screen and Goldmann Bowl Perimeter are good examples and are still used today in certain practices.

Computerized automated visual field testing became more popular which utilized static "white-on-white" stimulus presentation. The size and location of the test target remain constant. The retinal sensitivity or threshold at the specific location is determined by varying the brightness of the test target. The shape of the hill of vision is defined by repeating the threshold measurement at various locations in the field of vision. The result is highly quantifiable and sensitive.

Newer test algorithms have resulted in testing strategies such as SWAP (Short Wavelength Automated Perimetry) or "blue on yellow" perimetry (Humphrey). This method presents blue static stimuli on a uniform yellow background, intended to test a smaller population of retinal neurons that selectively respond to those colour wavelengths. The test is thought to potentially reveal visual field loss 5 to 6 years ahead of traditional white-on-white automated perimetry, but it requires a significant longer testing times.

FASTPAC, SITA (Swedish Interactive Testing Algorithm) Standard, SITA Fast (Humphrey) are tests which use intelligent analysis of the patient's responses and age-normed statistical data to significantly shorten the testing time. There may be some limitations in term of analysis of field loss progression, as well as limitation on the number of missed point re-test, but statistical correlation with traditional threshold testing is good.

The other test algorithms used in kinetic Fixation Perimetry (Dicon). A feature unique to those perimeters is that the patient is constantly looking at the moving fixation target during testing. This feature has been found to make the visual field testing more comfortable for the patient.

1.4.1 Visual Field Loss in Glaucoma

Up to 50% of the optic nerve fibers can be destroyed in glaucoma patients before the visual field defect manifests in perimetry, therefore regular visual field measurement is critical. Furthermore the visual field data alone cannot be an indicator of possible glaucoma. Careful and regular monitoring of optic nerve cupping and IOP are imperative in determining changes. It can take up to 4 to 6 years before ganglion cell damage will be detectable on visual field.

Generalized defects are caused by diffuse loss of axons, often associated with concentric enlargement of the cup and diffuse generalized thinning of the rim tissue. Generalized depression (decreased in sensitivity) of the visual field and increase in variability (increased short-term fluctuation) may be early signs of glaucomatous damage. However these changes are not specific to glaucoma and may result from other factors, for example, incorrect refraction during the test, aging, media opacities, small pupil and inattentiveness of the patients.

Localized visual field defects within the central 30 degrees are the most easily identified and have the most characteristic types of field abnormalities associated with glaucoma. They are related to localized atrophy of the nerve fiber bundles at the superior and/or

inferior poles of the optic disc, which are the most typically affected in the early stages of glaucomatous damage. The inferior pole is more preferentially affected, resulting in a superior scotoma in the upper arcuate ares (the Bjerrum area).

Arcuate scotomas arch around fixation, corresponding to the course of the arcuate nerve fiber bundles. They are usually positioned within 10 to 20 degrees of fixation, at first not connected to the blind spot (paracentral scotoma) and then extending temporally toward the blind spot following the course of the nerve fiber bundle to the horizontal raphe (arcuate scotoma).

The nasal step is characterized by nerve fiber loss that is usually most marked at the inferior pole and next most marked at the superior pole of the optic disc. The disc with more marked cupping inferiorly than superiorly will frequently have a superior nasal loss, the defect above the horizontal raphe is more denser than below the horizontal raphe.

The temporal wedge-shaped defect is not common. Localized loss of tissue on the nasal side of the optic disc may occur early in glaucoma, resulting in a temporal wedge-shaped lesion. An altitudinal field defect without encroachment upon fixation involves two horizontal quadrants but respects the horizontal meridian represent an advanced stage of glaucomatous damage.

In the late course of glaucomatous optic nerve damage, a central island and/or temporal island of vision is typically preserved. A split of fixation is a results from encroachment

of an altitudinal field defect upon the point of fixation. Central and temporal islands of vision may persist for many years but will eventually be lost with sufficient intensity and duration of disease.

Therefore, once the patient has moderate glaucoma, visual field monitoring is important and becomes a reliable indicator of ganglion cell damage. However it must be remembered that despite the critical role, visual field testing is not without its clinical limitation. It is a subjective psychophysical test that is greatly influenced not only by disease but also by the response patterns of the patient (Lalle, 1993).

Ocular Hypertension Treatment (OHT) study involved following a group of 1636 high risk patients (ocular hypertensive) for 10 years (Keltner et al 2000). In this study the development of glaucoma and visual field defect was observed. The OHT study determined the following distribution of early visual field loss; arcuate partial (22%), arcuate complete (10%), paracentral (16%) nasal step (11%), generalized depression (9%), temporal edge (3%) and central (1%).

Visual field progression is the most important part of clinical management in chronic glaucoma because this is the outcome that affects the patient's quality of life. Changes in the visual field will make the physician consider a change in clinical management. The identification of visual field progression requires a series of field, usually more than three and often five or six. In many instances, the sudden change is not caused by glaucoma, but either vascular in origin, or due to changes in the visual pathways.

In the study to see the rate of progression in open-angle glaucoma it showed that treatment would slow the progression rate for all persons by 20% or would stop progression in 20% and have no effect in 80% of person (Quigley et al, 1996).

1.4.2 Grading Systems

Visual field interpretation is frequently difficult and requires a certain level of training and experience. Various grading systems have been developed and used as guidelines for visual field interpretation. Hodapp and co – workers (1993) proposed a classification based on defect extent and on proximity of defect to fixation point.

The Advanced Glaucoma Intervention Study (AGIS) proposed a classification whereby the visual field defect score is based on the number and depth of clusters of adjacent depressed test sites in the upper and lower hemifields and in the nasal area of the total deviation print out (AGIS, 1996). This scoring system is accurate, however for routine use it may be too elaborate.

In 1996, the Glaucoma Staging System (GSS) was introduced based on the two main perimetric global indices, Mean Deviation (MD) and Corrected Pattern Standard Deviation (PSD) or Corrected Loss Variance (CLV), plotted on an X – Y coordinate diagram. However, some problems were found from this system and it was modified based upon 9 years of clinical experience and become GSS 2 (Appendix 4).

In GSS 2, it classifies defects very similarly to the previous GSS and found to have a very high correlation rate between Hodapp – Parrish – Anderson and AGIS methods

which are much more time consuming (Brusini and Filacorda, 2006). It has several characteristic of an ideal glaucoma classification method and it can be used on a regular basis in providing a quick, reliable and standardized classification of functional damage in patients with glaucoma.

Frequency Doubling Technology Staging System 2 (FDT SS 2) (Appendix 4) is a version of previous FDT SS due to the new Humphrey Matrix Instrument provides MD and PSD values which are different from the previous version. It is a staging system specially created for FDT as a guideline that can be used to define FDT test abnormalities. FDT SS 2 is currently the only method, which provides the user with an immediate and reliable classification of both the severity and characteristics of visual field detected with the 30 – 2 or 24 – 2 Humphrey Matrix tests (Brusini, 2006).

1.5 FREQUENCY DOUBLING PERIMETRY (FDP)

The human retina has approximately 1.2 to 1.5 million neurons or also called retinal ganglion cell axons or nerve fibers that bundle together to comprise the optic nerve. The irreversible loss of these retinal nerve fibers occurs in glaucoma and other ocular conditions, associated with the classic gradual increase in optic nerve "cup" size over time.

Retinal nerve fibers can be simply classified into two main types that transmit signals from the retinal receptor cells to the lateral geniculate body and ultimately to the visual cortex. These are the Magno cellular (or M) cells and the Parvo cellular (or P) cells.

The M cell pathway is responsible for low – contrast, high temporal frequency (or motion) stimulus detection. For example, a black car rapidly passing by a driver's side window at night may stimulate the driver's M cell neurons. The P cell pathway is responsible for high contrast, low temporal frequency (or static) stimulus detection. An example would be a patient attempting to read the smallest letters possible on a standard projected Snellen eye chart.

The larger diameter M cell neurons constitute approximately 10% of the total number of retinal nerve fibers. It has been found that a particular M cell neurons sub – set comprising a third to half of the M cell neurons (called "non – linear" M cells) are usually the first to die in glaucoma and this unique pathological characteristic established the basis for frequency doubling testing.

When a low – spatial – frequency sinusoidal grating (less than one cycle per degree) undergo high – temporal – frequency counter phase flicker (greater than 15 Hz), the stimulus appears to have twice as many light and dark bars as are physically present (Maddess and Henry, 1992).

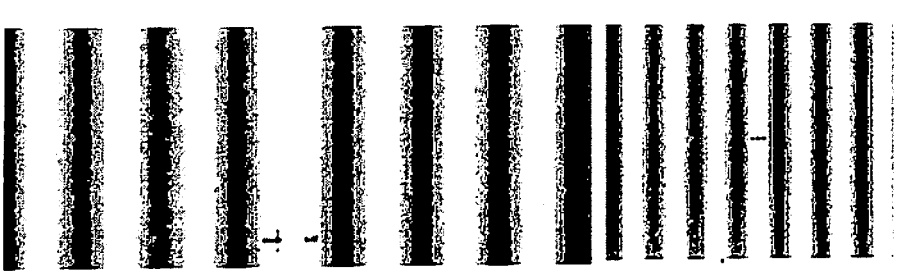


Figure 1.1 Frequency Doubling Illusion

High frequency (e.g., 20-30 Hz) alternation between light and dark bars (e.g., 1 cycle per degree) shown on the left two images creates the doubling illusion (2 cycles per degree grating) shown on the right image. (One cycle = light + dark bar.)

The phenomenon is known as the frequency doubling illusion in reference to the fact that the spatial frequency of the grating appears to be doubled. The frequency doubling illusion is generally believed to be generated by a non linearity present in the visual pathway (Maddess 1995). It is specifically mediated by the M cell , a subset of the retinal ganglion cells that project to the magno cellular layer of the lateral geniculate nucleus that have non – linear response properties.

According to Maddess and associates, the M – cell comprise about 27% of the magno cellular fibers and tend to have the largest diameter axons among retinal ganglion cells. It is the vulnerable "non – linear" M cell neurons that are thought to transmit the signal related to this illusion. Since the M cell neurons tend to be among the first to die (Maddess, 1992) selective testing by presenting alternate grating stimuli was developed in an attempt to identify earlier retinal neuron loss than by traditional automated perimetry.

FDP is by far one of the most widely used nonconventional methods of visual field testing currently available (Cello et al, 2000, Johnson et al, 1997, Maddess et al, 1992, Quigley, 1998).

The original FDP test uses stimulus patterns of sinusoid grating (alternate vertical dark and light bars) with low spatial frequency (0.25 c/d) and high temporal frequency counter phase flicker (25 Hz). The test results are given in both numerical format and statistical probability map (total and pattern deviation) formats. The Humphrey Matrix (Welch Allyn FDT, Skaneateless Falls, N Y and Carl Zeiss Meditec, Dublin, CA) represents the second generation of the original FDT perimeter. It offers new additional programs with a greater number of test points of different sizes and different spatial pattern (0.5 c/d) temporal frequency (18 Hz), whereas still offering the test found in the former instrument with enhanced threshold strategies (Anderson et al, 2005). The stimulus can be seen by patient in the screen as below (figure 1.2).

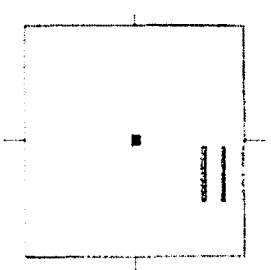


Figure 1.2: Stimulus on the screen

Stimulus as seen by patient on the screen. Center black square is the fixation target.

The FDP is a portable device that specifically tests for visual field loss due to non – linear M cell neuron death, typically from glaucoma. Since this instrument target is a specific sub – set of nerve fibers that transmit larger, low – contrast, motion – based stimuli rather than detailed high – contrast static stimuli, it able to tolerate up to 6 diopter of blur and is not affected by external room illumination or variations in the pupil size, as long as the pupil diameter is greater than 2 mm.

1.5.1 The Humphrey Matrix

The new Humphrey Matrix was released in April 2003. The recent advances in FDP Technology include; reducing target size from 10 to 5 to improve the instrument's ability to detect progression with excellent ability to locate early damage. There are two new FDT threshold tests, 24 – 2 (55 points) and 30 – 2 (69 points), two new FDT central threshold test, 10 – 2 and macula to evaluate patients with macular conditions.

The new 24 – 2 and 30 – 2 FDT threshold tests are similar to the tests of the same name of Humphrey Field Analyzer II (HFA II). These tests are recommended for patients being evaluated for glaucoma or ocular hypertension. The 24 – 2 FDT pattern (55 points) and the 30 – 2 FDT pattern (69 points) use a similar footprint with the most points tested in common. The 30 – 2 FDT test adds points in the periphery.

The 24 – 2 FDT test takes about 5 minutes and 30 – 2 FDT test takes about 6 to 7 minutes. Each test requires slightly more time (not more than 30 seconds) when test locations have visual field damage. Ten fixation checks using the Heijl Kraken method, ten false – positive and six false – negative trials are performed as reliability checks and displayed as a fraction as well as a percentage of the total.

The 10 – 2 and the Macula FDT test are used to evaluate individuals with conditions affecting the macular area. Both tests use 2x2 square targets with a spatial frequency of 0.5 cycles per degree for the sine wave grating and temporal frequency of 12 Hz. The spatial and temporal characteristics for the 10 – 2 and the macula test do not allow the

stimulus to appear to be frequency doubled, so the threshold determination is a flicker sensitivity response.

The screening test is used to assess rapidly the central visual field as part of the pre – examination battery of test. All Humphrey Matrix screening test results are automatically analyzed and compared to a normative database. There are two rapid screening procedures for two stimulus presentation patterns, the N – 30-5 and 24 – 2. If two or more locations are flagged, regardless of location or probability level, the test should be repeated immediately.

Field loss may be suspected if, upon repeat testing, two points are against marked with at least one of the identified points repeated from the initial test. If this occurs and there is no apparent reason for the screening loss, such as cataract or retinal condition, a threshold test is indicated. Depending on the test location and the severity of loss, a threshold test may be needed even if only one point is identified. The reliability indices should be reviewed as excess fixation losses or a high number of false positives may influence the test outcome.

As an overview, FDP provides a practical means of screening for glaucoma because of its rapidity and validity for glaucoma detection (Burnstein et al, 2000, Sponsel, 1988). Additionally, FDT perimetry theoretically tests a selective portion of the retinal ganglion cell systems and may be useful for early detection of glaucoma (Quigley, 1998).

POAG is widely known as the most prevalent types of glaucoma. It is a major health concern throughout the world because of its usually silent but progressive in nature and one of the leading preventable causes of blindness in the world. With appropriate screening and treatment, glaucoma can usually be identified and stopped before significant vision loss occurs.

This study was conducted to see the capability of FDP in the detection of visual abnormalities in POAG patients in comparison to the Humphrey Visual Field (HVF) which is taken as a gold standard. We aim to provide data which can be used as a screening tool for POAG in the population and for early detection of POAG therefore better management for prevention of blindness by early medical or surgical intervention can be instituted.

CHAPTER 2

OBJECTIVES

2.0 OBJECTIVES

2.1 GENERAL OBJECTIVE

To determine the capability of FDP in the detection of visual field abnormalities in POAG patients.

2.2 SPECIFIC OBJECTIVES

i. To determine the sensitivity and specificity of FDP in detecting visual field abnormalities in POAG patients.

ii. To determine the agreement between FDP and HVF analyzer in detecting visual field abnormalities in POAG patients.

CHAPTER 3

MATERIALS AND METHODS

3.0 MATERIALS AND METHODS

3.1 RESEARCH STRATEGY

Prospective, comparative, cross-sectional study.

3.2 POPULATION, SETTING AND TIME

Study population : POAG patients attending eye clinic in Hospital Universiti Sains Malaysia (HUSM), Kampus Kesihatan, Kubang Kerian, Kelantan.

Study place : Eye clinic HUSM

Duration of study : 21 months (January 2005 to September 2006)

3.3 SAMPLING AND SAMPLE SIZE

3.3.1 Sampling Method

A systematic random sampling was used to select patients that were diagnosed as POAG. Every first POAG patients who was attending eye clinic was selected (e.g. patient number 1, 3, 5, 7....).

3.3.2 Sample Size

Sample size calculated using single proportion formula:

$$n = \frac{1.96^2 \times p\,(1 - p)}{\Delta^2}$$

n = sample size

z = 95% confident interval which is 1.96

p = based on literature review by Burnstein Y, et al, (2000) the proportion (p) of sensitivity and specificity was estimated at 0.9 or 90%.

Δ = precision 5%

Calculated using single proportion formula:

n = 138 patients

Drop-out rate = 10%. Thus 138 x 110% = 150 patients

Sample size in this study = 150 patients

Drop-out sample is when the visual field testing is unreliable.

3.4 GRANT APPROVAL

3.4.1 Approved by the Research and Ethical Committee, School of Medical Sciences on 10th May 2005.

3.4.2 Approved by the Bio-Medical Sciences and Health Committee, Universiti Sains Malaysia, Pulau Pinang on 28th March 2006
(IRPA short-term grant number: 304/PPSP/6131440)

3.5 SELECTION CRITERIA

3.5.1 Inclusion Criteria

- POAG patients (new and follow up patients).
- Primary juvenile glaucoma with onset 10th to 35th year of life with family history.
- Consented for the study.

3.5.2 Exclusion Criteria

- Secondary open or closed angle glaucoma.
- Best corrected visual acuity less than 6/60 with Snellen.
- Eyes with retinal or optic nerve pathology which capable of producing a nerve fiber bundle defect.
- Handicapped and uncooperative patients who are unable to perform the test.

The confounding factors considered during patient selection were as follow:

1) Significant cataract which caused best corrected visual acuity (BCVA) of less than 6/60 will be excluded
2) Media opacities such as vitreous haemorrhage or significant corneal scar will be excluded.
3) History of ocular disease or surgery which can affect VF sensitivity.
4) Neurological disease other than glaucoma eg , pituitary lesion, demylinating disease or autoimmune diseases.
5) Retinal vasculopathy or retinopathy diseases eg, diabetic retinopathy, CRAO, CRVO, retinitis pigmentosa and ect which capable in causing VF defect.
6) Other type of optic neuropathy.

3.6 DEFINITION OF TERMS

3.6.1 Primary Open Angle Glaucoma (POAG)

Features: (Terminology and Guidelines for Glaucoma 2nd Edition European Glaucoma Society)

- Onset of glaucoma at the age of 35 years and above.
- Symptomatic until field loss advanced.
- IOP > 21mmHg without treatment.
- Optic nerve head with acquired characteristic glaucomatous damage and/ or retinal nerve fiber layer changes (diffuse or localized defects).
- Visual field with detectable glaucomatous defects corresponding to the optic disc damage may be present.
- Gonioscopy findings of open anterior chamber angle.

3.6.2 Visual Acuity (VA)

VA is defined as the ability to resolve fine detail in a pattern. VA can be expressed numerically in terms of the reciprocal of the size of the smallest resolvable detail. The letters on the chart have been design with the assumption that normal acuity corresponds to being able to resolve 1 minute of arc. The VA is measured by using Snellen chart reading from the distance of 6 meter. The best corrected VA is taken into record.