THE CORRELATION BETWEEN VISUAL ELECTROPHYSIOLOGY TEST WITH RETINAL NERVE FIBRE LAYER THICKNESS AND ADVANCE GLAUCOMA INTERVENTIONAL STUDY SCORE IN PRIMARY ANGLE CLOSURE GLAUCOMA PATIENTS.

by

DR. AHMAD NURFAHMI B. AKHTAR ALI
MBBS (MALAYA)

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (OPHTHALMOLOGY)

SCHOOL OF MEDICAL SCIENCES
UNIVERSITI SAINS MALAYSIA
2014

TABLE OF CONTENTS

CHAPTER THREE

CHAPTER FOUR

CHAPTER FIVE

CHAPTER SIX

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABREVIATIONS

AGIS	Advance Glaucoma Interventional Study
CCT	Central corneal thickness
DTL	Dawson-Trick-Litzkow electrodes
HFA	Humphrey Visual Field Analysis
HUSM	Hospital Universiti Sains Malaysia
IOP	Intraocular Pressure
MD	Mean difference
OCT	Ocular Coherence Tomography
OHT	Ocular Hypertension
ONH	Optic Nerve Head
PAC	Primary Angle closure
PACG	Primary Angle Closure Glaucoma
PERG	Pattern Electroretinogram
POAG	Primary Open Angle Glaucoma
PSD	Pattern Standard Different
PVEP	Pattern Visual Evoked Potential
RGC	Retinal Ganglion Cell
RNFL	Retina Nerve Fibre Layer
VFI	Visual Field Index

ABSTRAK

PENGENALAN

'Primary angle closure glaucoma (PACG)' menyebabkan masaalah kebutaan yang tinggi di kalangan masyarakat di Asia. Diagnosa dan pemantauan penyakit ini masih lagi mencabar disebabkan masalah perbezaan di antara struktur and fungsi di dalam penilaian kepala saraf optic (ONH) dalam penyakit PACG. Electrophysiology penglihatan (pattern electroretinogram (PERG) dan pattern visual evoked potential (PVEP)) mempunyai kemampuan dalam mengesan kerosakan fungsi 'retina ganglion cells (RGC)'. Ia mempunyai potensi sebagai ujian pelengkap kepada ujian struktur dan fungsi ONH sekarang bagi memantau penyakit glaucoma secara amnya dan penyakit PACG secara khusus.

OBJEKTIF

Penkajian keatas maklumbalas ujian electrophysiology penglihatan dan lapisan urat saraf retina (RNFL) dalam pesakit PACG. Korilasi di antara ujian tersebut dengan ketebalan RNFL dan 'Advance Glaucoma Interventional Study (AGIS)' turut dikaji.

METODOLOGI DAN BAHAN

Satu kajian hirisan lintang telah dijalankan di Hospital University Sains melibatkan 66 orang subjek daripada pesakit PACG dan normal. Pemeriksaan lengkap dijalankan bagi pengesahan penyakit PACG. Ujian struktur RNFL di ONH dilakukan menggunakan Cirrus SD-OCT (Carl Zeiss Meditec Inc, USA) dengan kekuatan penunjuk yang bagus ($\geq$ 6/10), PERG (size 'checks'0.8º) dan PVEP (size 'checks'0.25º) dilakukan oleh juru teknik yang terlatih. Analisa dilakukan dengan menggunakan 'Independent t-test', 'ANCOVA' dan 'Pearson's correlation coefficient'.

KEPUTUSAN

Terdapat signifikasi statistik pengurangan ‘amplitude’ dan ‘latency’ PERG dalam pesakit PACG ($p<0.001$). Terdapat juga signifikasi statistik pengurangan keamatan pada ‘amplitude’ ($p<0.001$) dan pengurangan tempoh ‘latency’ ($p<0.001$) P100 bagi ujian PVEP. Pesakit PACG menunjukkan terdapat signifikasi statistik mempunyai saiz ‘disc area’ yang lebih kecil (2.03 ± 0.26) , berbanding normal (2.27 ± 0.35). Terdapat signifikasi statistik pengurangan ketebalan RNFL di setiap bahagian pada ONH dalam pesakit PACG ($p<0.001$). Ketebalan RNFL menunjukkan signifikasi statistik korilasi yang positif dengan ‘latency’ N95 ($r = 0.54$, $p = 0.001$) daripada PERG. Skor AGIS pula menunjukkan signifikasi statistik korilasi yang negative dengan N35 ($r = - 0.36$, $p = 0.041$) dan N95 ($r = - 0.49$, $p = 0.003$) daripada ujian PERG. Positif dan negative korilasi juga didapati di antara ketebalan RNFL dan skor AGIS bagi ujian PVEP di kalangan pesakit PACG, namun tiada signifikasi statistik ditunjukkan.

KESIMPULAN

Electrophysiology penglihatan menunjukkan perubahan yang signifikasi tehadap para pesakit PACG. Terdapat signifikasi statistik korilasi di antara PERG dan penilaian struktur RNFL pada ONH yang kebiasaanya dilakukan. PERG mempunyai potensi sebagai ujian alternative bertujuan memantau perubahan pada fungsi saraf (ONH) pada pesakit PACG.

KATA KUNCI

‘Primary angle closure glaucoma (PACG)’ , pattern electroretinogram (PERG), pattern visual evoked potential (PVEP), lapisan urat saraf retina (RNFL) Advance Glaucoma International Study (AGIS).

ABSTRACT

INTRODUCTION

Primary angle closure glaucoma (PACG) causes more blindness in Asian population. Diagnosis and monitoring remains a challenge especially due to structural-functional discrepancy in evaluating optic nerve head (ONH) in PACG. Visual electrophysiology (pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP)) has the capability in detecting functional impairment of retina ganglion cells (RGC). It has the potential as complimentary test to the existing standard structural and functional test for ONH evaluation in glaucoma in general and PACG specifically.

OBJECTIVE

To evaluate visual electrophysiology response and retina nerve fibers layer (RNFL) thickness in PACG. The correlation between visual electrophysiology with the glaucoma severity based on RNFL thickness and Advance Glaucoma Interventional Study (AGIS) score were also evaluated.

MATERIALS AND METHODS

A comparative cross sectional study was conducted in Hospital University Sains Malaysia involving 66 samples of PACG patients and controls. A Complete ocular assessment was done to confirm the diagnosis of PACG. Evaluation of structural changes of RNFL of ONH was conducted using Cirrus SD-OCT (Carl Zeiss Meditec Inc, USA) with good signal strength ($\geq$ 6/10).AGIS score was performed on a reliable reproducible visual field of two consecutive Humphrey's visual field (24-2) analysis. PERG (0.8^{o} checks size) and PVEP

(0.25º checks size) was conducted by a trained technician. Independent t-test, ANCOVA and Pearson's correlation coefficient analysis were used in analysis.

RESULTS

There was statistically significant reduction in amplitude and latency in of PERG in PACG patients ($p<0.001$). There was also significant reduction in magnitude of amplitude ($p<0.001$) and shorten of P100 latency in PVEP ($p<0.001$). PACG patients had significant smaller disc area (2.03±0.26) compared to controls (2.27±0.35). There was also significant thinner RNFL analysis in all quadrant of the ONH in PACG patients ($p<0.001$). RNFL thickness shown a significant strong positive correlation with the PERG amplitude of N95 ($r = 0.54$, $p = 0.001$). AGIS score showed a significant negative correlation between N35 ($r = - 0.36$, $p = 0.041$) and N95 ($r = - 0.49$, $p = 0.003$) of PERG. Similarly the positive and negative correlations were seen between RNFL thickness and AGIS score respectively with PVEP. However it was not statistically significant.

CONCLUSION

Visual electrophysiology showed significant changes in PACG patients. There was significant correlation between PERG and existing standard structural and functional analysis of ONH. PERG is the potential alternative tools for evaluation of functional changes of ONH in PACG patients.

KEY WORDS

'Primary angle closure glaucoma (PACG)', pattern electroretinogram (PERG), pattern visual evoked potential (PVEP), retina nerve fiber layer (RNFL), Advance Glaucoma International Study (AGIS).

THE CORRELATION BETWEEN VISUAL ELECTROPHYSIOLOGY TEST WITH RETINA NERVE FIBRE LAYER THICKNESS AND ADVANCE GLAUCOMA INTERVENTIONAL STUDY SCORE IN PRIMARY ANGLE CLOSURE GLAUCOMA PATIENT.

Dr Ahmad Nurfahmi Akhtar Ali

MMed Ophthalmology

Department of Ophthalmology

School of Medical Sciences, University Sains Malaysia

Health Campus,16150 Kelantan, Malaysia

INTRODUCTION: Primary angle closure glaucoma (PACG) causes more blindness in Asian population. Diagnosis and monitoring remains a challenge partly due to discrepancy between structural and functional changes in evaluating optic nerve head (ONH) in PACG. Visual electrophysiology (pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP)) has the capability in detecting early functional impairment of retina ganglion cells (RGC). Perhaps, it has the potential as complimentary test to the existing standard structural and functional test for ONH evaluation in glaucoma in general and PACG specifically.

OBJECTIVE: To evaluate visual electrophysiology response and retina nerve fibers layer (RNFL) thickness in PACG. The correlation between visual electrophysiology with the glaucoma severity based on RNFL thickness and Advance Glaucoma Interventional Study (AGIS) score were also evaluated.

MATERIALS AND METHODS:A case control study was conducted in Hospital Universiti Sains Malaysia involving 33 of PACG patients and 33 controls. A complete ocular assessment was done to confirm the diagnosis of PACG. Evaluation of structural changes of RNFL of ONH was conducted using SD-OCT (Carl's Zeiss) with minimal signal strength more than 6/10.

AGIS score was performed on a latest reliable reproducible of two consecutive Humphrey's visual field (SITA-Standard) 24-2 analysis. Pattern electroretinogram (PERG), 0.8º (48 min of arc) and pattern visual evoked potential (PVEP), 0.25º (15 min of arc) were performed. Independent t-test and ANCOVA analysis were used to compare the parameters. Pearson's correlation coefficient was used to correlate the parameters and RNFL thickness as well as AGIS score.

RESULTS: There was statistically significant reduction in amplitude and latency in of PERG in PACG patients ($p<0.001$). There was also significant reduction in magnitude of amplitude ($p<0.001$) and shorten of P100 latency in PVEP ($p<0.001$). PACG patients had significant smaller disc area compared to controls (2.03±0.26, 2.27±0.35, $p =0.001$). There was also significant thinner RNFL analysis in all quadrant of the ONH in PACG patients ($p<0.001$). RNFL thickness shown a significant strong positive correlation with the PERG amplitude of N95 ($r = 0.54$, $p = 0.001$). AGIS score showed a significant negative correlation between N35 ($r = -0.36$, $p = 0.041$) and N95 ($r = - 0.49$, $p = 0.003$) of PERG. Similarly the positive and negative correlations were seen between RNFL thickness and AGIS score respectively with PVEP. However it was not statistically significant.

CONCLUSION: Visual electrophysiology showed reduced response in PACG patients. There was correlation established between PERG and existing standard structural and functional analysis of ONH. PERG is the potential alternative tools for evaluation of functional changes of ONH in PACG patients.

Assoc. Prof. Dr. Wan Hazabbah Wan Hitam

Assoc. Prof. Dr. Liza Sharmini Ahmad Tajudin (Co-Supervisor)

ABSTRACT

INTRODUCTION

Primary angle closure glaucoma (PACG) causes more blindness in Asian population. Diagnosis and monitoring remains a challenge partly due to discrepancy between structural and functional changes in evaluating optic nerve head (ONH) in PACG. Visual electrophysiology (pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP)) has the capability in detecting early functional impairment of retina ganglion cells (RGC). Perhaps, it has the potential as complimentary test to the existing standard structural and functional test for ONH evaluation in glaucoma in general and PACG specifically.

OBJECTIVE

To evaluate visual electrophysiology response and retina nerve fibers layer (RNFL) thickness in PACG. The correlation between visual electrophysiology with the glaucoma severity based on RNFL thickness and Advance Glaucoma Interventional Study (AGIS) score were also evaluated.

MATERIALS AND METHODS

A case control study was conducted in Hospital Universiti Sains Malaysia involving 33 of PACG patients and 33 controls. A complete ocular assessment was done to confirm the diagnosis of PACG. Evaluation of structural changes of RNFL of ONH was conducted using HD-OCT (Carl's Zeiss) with minimal signal strength more than 6/10.

AGIS score was performed on a latest reliable reproducible of two consecutive Humphrey's visual field (SITA-Standard) 24-2 analysis. Pattern electroretinogram (PERG), 0.8º (48 min of arc) and pattern visual evoked potential (PVEP), 0.25º (15 min of arc) were performed. Independent t-test and ANCOVA analysis were used to compare the parameters. Pearson's correlation coefficient was used to correlate the parameters and RNFL thickness as well as AGIS score.

RESULTS

There was statistically significant reduction in amplitude and latency of PERG in PACG patients ($p<0.001$). There was also significant reduction in magnitude of amplitude ($p<0.001$) and shorten of P100 latency in PVEP ($p<0.001$). PACG patients had significant smaller disc area compared to controls (2.03 ± 0.26, 2.27 ± 0.35, $p=0.001$). There was also significant thinner RNFL analysis in all quadrant of the ONH in PACG patients ($p<0.001$). RNFL thickness shown a significant strong positive correlation with the PERG amplitude of N95 ($r = 0.54$, $p = 0.001$). AGIS score showed a significant negative correlation between N35 ($r = - 0.36$, $p = 0.041$) and N95 ($r = - 0.49$, $p = 0.003$) of PERG. Similarly the positive and negative correlations were seen between RNFL thickness and AGIS score respectively with PVEP. However it was not statistically significant.

CONCLUSION

Visual electrophysiology showed reduced response in PACG patients. There was positive correlation established between PERG and existing standard functional analysis and negative correlation with structural analysis of ONH. PERG is the potential alternative tools for evaluation of functional changes of ONH in PACG patients.

KEY WORDS

'Primary angle closure glaucoma (PACG)', pattern electroretinogram (PERG), pattern visual evoked potential (PVEP), retina nerve fiber layer (RNFL), Advance Glaucoma International Study (AGIS).

ABSTRAK

PENGENALAN

Glaucoma sudut tertutup primer (PACG) menyebabkan masalah kebutaan yang tinggi di kalangan masyarakat di Asia. Diagnosa dan pemantauan penyakit ini masih lagi mencabar disebabkan masalah perbezaan di antara struktur and fungsi di dalam penilaian kepala saraf optik (ONH) dalam penyakit PACG. Electrophysiologi penglihatan (‘pattern electroretinogram (PERG)’ dan ‘pattern visual evoked potential (PVEP)’) mempunyai kemampuan dalam mengesan kerosakan fungsi cell-cell ganglion retina (RGC). Ia mempunyai potensi sebagai ujian pelengkap kepada ujian struktur dan fungsi ONH sekarang bagi memantau penyakit glaucoma secara amnya dan penyakit PACG secara khusus.

OBJEKTIF

Penkajian keatas maklum balas ujian electrophysiology penglihatan dan lapisan urat saraf retina (RNFL) dalam pesakit PACG. Korilasi di antara ujian tersebut dengan ketebalan RNFL dan ‘Advance Glaucoma Interventional Study (AGIS)’ turut dikaji.

METODOLOGI DAN BAHAN

Satu kajian pengawalan kes telah dijalankan di Hospital University Sains melibatkan 66 orang subjek daripada pesakit PACG dan normal. Pemeriksaan lengkap dijalankan bagi pengesahan penyakit PACG. Ujian struktur RNFL di ONH dilakukan menggunakan Cirrus HD-OCT (Carl Zeiss Meditec Inc, USA) dengan kekuatan penunjuk yang bagus (≥ 6/10), PERG (size

'checks'0.8º) dan PVEP (size 'checks'0.25º) dilakukan oleh juruteknik yang terlatih. Analisa dilakukan dengan menggunakan 'Independent t-test', 'ANCOVA' dan 'Pearson's correlation coefficient'.

KEPUTUSAN

Terdapat signifikasi statistik pengurangan 'amplitude' dan 'latency' PERG dalam pesakit PACG ($p<0.001$). Terdapat juga signifikasi statistik pengurangan keamatan pada 'amplitude' ($p<0.001$) dan pengurangan tempoh 'latency' ($p<0.001$) P100 bagi ujian PVEP. Pesakit PACG menunjukkan terdapat signifikasi statistik mempunyai saiz 'disc area' yang lebih kecil berbanding normal (2.03 ± 0.26, 2.27 ± 0.35, $p =0.001$). Terdapat signifikasi statistik pengurangan ketebalan RNFL di setiap bahagian pada ONH dalam pesakit PACG ($p<0.001$). Ketebalan RNFL menunjukkan signifikasi statistik korilasi yang positif dengan 'latency' N95 ($r = 0.54$, $p = 0.001$) daripada PERG. Skor AGIS pula menunjukkan signifikasi statistik korilasi yang negatif dengan N35 ($r = - 0.36$, $p = 0.041$) dan N95 ($r = - 0.49$, $p = 0.003$) daripada ujian PERG. Positif dan negatif korilasi juga didapati di antara ketebalan RNFL dan skor AGIS bagi ujian PVEP di kalangan pesakit PACG, namun tiada signifikasi statistik ditunjukkan.

KESIMPULAN

Electrophysiology penglihatan menunjukkan perubahan yang signifikasi tehadap para pesakit PACG. Terdapat signifikasi statistik korilasi yang positif di antara PERG dan penilaian struktur RNFL pada ONH dan juga signifikasi korelasi yang negatif dengan ujian penilian fungsi medan penglihatan yang kebiasaanya dilakukan. PERG mempunyai potensi sebagai ujian alternatif bertujuan memantau perubahan pada fungsi saraf (ONH) pada pesakit PACG.

KATA KUNCI

'Primary angle closure glaucoma (PACG)' , pattern electroretinogram (PERG), pattern visual evoked potential (PVEP), lapisan urat saraf retina (RNFL) Advance Glaucoma International Study (AGIS).

Introduction

1.1 Primary angle closure glaucoma (PACG).

Primary angle closure glaucoma (PACG) generally affects more Asians as compared to their Western counterparts. However, primary open angle glaucoma (POAG) is still the predominant type of glaucoma in Asian population (Hu Z et al., 1989; Quigley HA et al., 1996; Foster PJ et al. 2002). Quigley HA et al. (2006) had reported that total of 60.5 million people with glaucoma in 2010 and expected the prevalence will increase to 79.6 million by 2020. From the same report, in 2010, 26% of glaucoma was angle closure with Asians and women represented 87% and 70% of those with angle closure. They also reported on bilateral blindness involved 3.9 million people with angle closure in 2010 and expected to increase to 5.3 million people in 2020. Shen et al. (2008) in the Singapore Malay Eye Study had reported the epidemiological review of PACG in South-East Asia, with highest prevalence noted in Myanmar, followed by Thailand and Singapore.

The term PACG is defined as present of progressive optic neuropathy resulted from degenerative changes of retina ganglion cells (RGC) and present of occludable angle structures of more than 270^0, associated with raised intraocular pressure (IOP) (Foster PJ et al. 2002). This could explain why the symptoms are more manifest in PACG rather than POAG. Should a rise in IOP happen suddenly, patient would experience acute attack or also known as acute PACG which is an emergency. Primary angle closure (PAC) and primary angle closure suspect (PACS) is another spectrum of the disease. PAC is by definition is an eye without glaucomatous optic neuropathy

but with occludable angle structures of more than 270^0 withfeatures indicating present of trabecular obstruction by the peripheral iris has occurred, such as high intraocular pressure as well as peripheral anterior synechiae, iriswhorling (distortion of the radially orientated iris fibres), glaucomfleken and excessive pigment deposition on the trabecular surface (Foster PJ et al. 2002). While PACS is an eye with occludable angle structures of more than 270^0 only, and does not have glaucomatous optic neuropathy or evidence of trabecular obstruction occurred (Foster PJ et al. 2002).

The pathogenesis of PACG involves either the pupillary block or non-pupillary mechanism, with the both mechanisms having the risk of acute attack, although the pupillary block is still the commonest mechanism observed (Robert N. et al., 2014). Obstruction of aqueous flow at the pupillary area had caused accumulation of fluids behind the iris which precipitated posterior pushing mechanism, thus iris convexity is increased hence created a shallow anterior chamber and obstructed the aqueous of outflow pathway. Previously Quigley HA et al. (1984) and Marx MS et al. (1998) had demonstrated involvement of magnocelluar and parvocellular pathway damage in glaucoma. They concluded that magnocellular was exclusively affected while the parvocellular was spared, with the X cells subgroup were more affected than the Y cells. Their experimental models had proven it especially in early stage glaucoma and those with history of angle closure. In chronic progressive disease especially POAG they reported involvement of both pathways. However recent review by Bach M et al. (2008) this pathway involvement theory had showed inconsistent reports from few latest studies. They also highlighted the issues regarding the early blue deficits in glaucoma cannot readily be explained with the involvement of

magnocellular pathway alone. So, they had suggested studying more on isolation of retinal ganglion cell activity in glaucoma patients.

During an acute angle closure attack, a very high intraocular pressure (usually more than 30mmHg) is recorded. It is also associated with other clinical symptoms such as very marked ocular pain, nausea, vomiting, and intermittent blurring of vision with haloes in the patient (Robert N. et al., 2014). Other than that, the increased IOP level has trek capability of causing mechanical structural damage to the RGC and nerve fibre layer (NFL) (Boland et al., 2007). Nevertheless, ocular perfusion to the optic nerve head is possibly compromised by affecting its auto-regulation earlier during the acute attack.

Other ocular risk factors for angle closure include a small eye with short axial length and with crowded anterior segment, a shallow central anterior chamber depth, and more anteriorly positioned thicker lens had been reported in several studies (Sakai H et al., 2005; Lavanya R et al., 2008; Nongpiur ME et al. 2011). A recent study by Vithana EN et al. (2012) reported a genome-wide association study which included more than 20 000 individuals from 7 countries. 3 new genetic loci for angle closure: was discovered: rs11024102 at *PLEKHA7*, rs3753841 at *COL11A1* (HGNC:2186), and rs1015213 located between *PCMTD1*(HGNC:30483) and *ST18* (HGNC:18695) on chromosome 8q. The findings demonstrate that genetically there is a difference between patients with PACG and POAG. However, the definite role and phenotypically behaviour of these genes towards retinal ganglion cells (RGC) and optic nerve is still under study.

1.2 Natural of Primary angle closure glaucoma (PACG)

Lowering of intraocular pressure (IOP) is the only proven strategy in treating glaucoma as it is the only modifiable risk factor in glaucoma (Boland MV et al., 2013). In Early Manifest Glaucoma Trial which is a multicentre randomised control trial evaluating progression of glaucoma in early glaucoma patients with and without treatment (Heijl A et al., 2002). The study showed that after 6 years of follow-up, the progression is more in patients without treatment as compared to those in the treatment group (62% vs 45%). The progression risk was doubled in those without treatment. This study however, was conducted on patients with POAG only.

In angle closure glaucoma, several treatment options can be instituted to deepen the anterior chamber and/or widen the outflow pathway at the angles. During an acute attack, definitive treatment that is laser peripheral iridotomy (LPI) or clear lens extraction (Lam DSC et al., 2007) is performed besides the standard treatment of topical IOP-lowering agent medications. Aung T et al. (2001) in their prospective study of acute angle closure in Asian had reported up to 72% success rate with LPI performed during an acute attack. An earlier study by Alsagoff Z et al. (2000) also reported a high success rate of LPI in treating an acute attack; however the presence of extensive peripheral anterior synechiae and preceded glaucomatous optic neuropathy had reduced its IOP lowering effect. Argon laser iridoplasty is an alternative to LPI in acute attack, and should any of these fail to control the IOP, surgical peripheral iridotomy or anterior chamber paracentesis are the other options available (Robert N. et al., 2014). However, the complication

of decompression retinopathy needs to be addressed should these procedure are performed (Fechtner RD et al., 1992;Dudley DF et al., 1996;Nah G et al. 2000).

A paper by Liza-Sharmini AT et al. (2014) which studied the clinical presentation, severity and progression of primary angle closure in local Malays, had reported almost 50% of their patients had history of an acute attack, while, 58% of their patients were diagnosed with PACG at initial presentation with incidence of blindness at almost 30%. Nevertheless, the study had concluded that chronic and asymptomatic PACG in local patients had contributed to more severe stage of PACG during initial ophthalmology visit due to their late presentation. The incidence of blindness in PACG reported in the study however, had almost similar incidence to those of ethnic Chinese in Singapore (Foster PJ et al., 2000) as well as the Indians in Southern India (Vijaya L et al., 2008). Robert N. et al. (2014) in their review had also reported only a third of PACG patients presented acutely with an angle closure attack and conclude that PACG is predominantly an asymptomatic disease with patients often unaware until the later stages of the condition. Thus, PACG patients are at a potentially higher risk of blindness when this spectrum is taken into consideration.

1.3 Progression of primary angle closure glaucoma (PACG)

In monitoring PACG, the concept is the same as monitoring other type of glaucoma, which is by monitoring anatomical structural abnormality of optic nerve head retinal nerve fiber layer (RNFL) and visual field functional damage resulting from the disease (Chen HY et al., 2011; Wollstein G et al., 2012) . Quantifying the optic nerve head changes is a great challenge, as most of PACG patients have short axial length. This is associated with crowded and variable optic disc morphology (Boland MV et al., 2013). Previously, the standard procedure of evaluating optic nerve head using vertical cup disc ratio (VCDR) is by direct visualization of the optic disc through direct ophthalmoscopy, slit lamp or binocular indirect ophthalmoscopy, or by stereoscopic picture from fundus photography (Chen HY et al.,2011; Wollstein G et al.,2012). All these methods are very subjective and entirely operator dependent. In an overcrowded disc, there is even more tendency to underestimate the VCDR by using the above methods.

With rapid advances in technology, ocular imaging modalities such as Optical Coherence Topography (OCT) and Heidelberg Retinal tomography (HRT) allow sensitive and accurate early detection of structural changes in optic nerve head RNFL (Martus P et al.,2000; Arkin RV et al.,2010; Chen HY et al., 2011). However, these tests have also been reported to have a structural-functional assessment discrepancy between optic nerve head RNFL thickness and the visual field test (Martus P et al.,2000; Arkin RV et al.,2010). Another later study by Wollstein G et al. (2012) in their study evaluating the threshold value in structural assessment and visual field had reported that visual field lost is demonstrated only after almost 20% to 40% structural damage has occurred.

Besides posterior segment structural and functional assessment, Nongpiur ME et al. (2011) highlighted that anterior segment assessment has greater significance in PACG as compared to POAG. Smaller anterior chamber width, area and volume, thicker irides with greater iris curvature, and lens vault is significant in PACG, and predispose the patient to have both acute and acute on chronic angle closure.

Several imaging methods that can be used to objectively assess eyes for the presence of angle closure have been recently developed. Ultrasound biomicroscopy (UBM) allows assessment of anterior chamber together with visualization of posteriorly located structures such as the ciliary body, lens zonules, and the anterior choroid. Another imaging is anterior segment optical coherence tomography (AS-OCT), which is a noncontact imaging device that acquires high-resolution cross-sectional images of the anterior chamber that allows rapid measurement of anterior segment parameters. These devices have been reported to have a higher rate in diagnosing angle closure as compared to conventional gonioscopy (Sakata LM et al.,2008; Wong HT et al., 2009).

1.4 Optical Coherence Tomography (OCT) in PACG

Optical coherence tomography (OCT) and scanning laser ophthalmoscopy have become important diagnostic tools for detection of glaucoma especially both in screening and in the early stage (Parikh RS et al., 2007; Alencar LM et al., 2008; Medeiros FA et al., 2008; Leite MT et al., 2010). The commonly used Cirrus Spectral Doman OCT (HD-OCT) has been demonstrated to be a consistent and clinically more accurate tool to determine optic disc parameters in a few studies (Manassakorn A et al., 2007; Sharma A et al., 2008; Leung CK et al., 2011).

Due to differences in ocular biometry, pathophysiology and IOP influence, many clinicians and researchers had thought the effect to and the characteristic of optic neuropathies is different in PACG as compared to other subtype of glaucoma. Douglas GR et al. (1975) in a study of 22 persons, accessing the morphological changes in optic nerve head (ONH) reported that after acute attacks of PACG, the ONH was pale and not deeply excavated; however for those same PACG patients after longer and more modest IOP elevation, the ONH characteristics were more similar to eyes with POAG. In contrast, Shen SY et al. (2006) reported in their study that the ONH features following acute angle closure were similar to eyes with POAG.

Previously, Sihota et al. (2005 and 2006) in the two studies had evaluated the structural changes in ONH analysis to differentiate between POAG and PACG. They had studied the difference between ONH parameters measured using OCT as well as HRT to compare normal, POAG, and PACG eyes in an East Indian population. They had reported OCT measurement demonstrated significant differences in PACG group, with less rim area, disc cupping area, cup volume, cup-to-disc (C/D) ratios, and the optic disc cup shape as compared to POAG and normal. This is perhaps the evidence that PACG exclusively has a different ONH structural as compare to other glaucoma subtype.

OCT allows direct measurement of RNFL thickness by in vivo visualization of the retina and optic nerve head (ONH) (Sommer A et al., 1991; Chen TC et al., 2008). Budenz DL et al., (2005) have studied the sensitivity and specificity of OCT measurement in glaucoma. From their study, it is concluded that OCT measurement of RNFL is accurate in glaucoma with visual field defect. Later, Boland MV et al. (2008) in their study comparing POAG and PACG by OCT parameters had reported the mean total RNFL in PACG was thicker compared to POAG. Based on this study finding, the authors highlighted the possibility of differences in the characteristics of OCT parameters in PACG. However, further longitudinal study considering confounding factors such as age and severity of the disease should be done.

1.5 The visual field defect and Staging of Glaucoma

Perimetric glaucoma may be graded on their visual field sensitivities as measured by standard automated perimetry (SAP) based on the depth and number of defective points, mean deviation (MD), pattern standard deviation (PSD) and the most recent, visual field index (VFI). This is important in staging the severity of glaucoma, monitoring the progression and assisting clinical investigators who are studying new forms of treatment response in glaucoma (Speath GL et al., 2005).

Rhee K et al. (2001) had done a comparative study between visual field defects in POAG and PACG patients. The study had reported there is a different pattern of visual field defects noted between the two. They had concluded that PACG has a tendency towards more diffuse damage rather than localised defects as seen more commonly in POAG. The study however, only reported in early and moderate stage of glaucoma; advanced stage patients were not studied. Later, Gazzard G et al. (2003) had conducted a study assessing the relation between IOP and visual field defect in PACG and POAG. This study found a stronger association between pre-treatment IOP and visual field defect in PACG than in POAG. Nevertheless, Boland MV et al. (2008) had stated that there was no correlation established between field defects in both POAG and PACG with the ONH structure.

The Advanced Glaucoma Intervention Study (AGIS) investigators used a graduated scoring system (0 to 20 points) to denote the visual field deterioration in their patients (AGIS investigators, 1994). The score is obtained from the total deviation plot of Humphrey Visual Field Statpac2 (24-2). Once a visual field point reached the minimal amount of sensitivity depression, that particular point is considered defective, and then a score will be given (Mills et al., 2006). This scoring system however, is impractical for routine clinical use. Presence of media opacity such as significant cataract or cornea opacity can give a false score, due to defective point changes detected in total deviation. Moreover, early diffuse glaucomatous changes can be missed by this scoring (Susanna Jr. R et al., 2009).

1.6 Pattern Electroretinogram (PERG) and glaucoma.

In glaucoma, visual field losses are only demonstrated after at least 25-30% of retina ganglion cells (RGC) are lost. (Quigley HA et al., 1999;Kerrigan–Baumrind LA et al.,2000). This has given rise to structural-function discrepancy especially in the early stage of the disease. With the ability of PERG ability to detect compromised and lost RGC, diagnosis of the early stages of glaucoma could perhaps be established earlier to prevent the delay in starting treatment, hence reducing the risk of blindness (Parisi V et al., 2001 and 2006; Bach M et al., 2007) . The role of PERG in glaucoma is in early detection, monitoring the disease progression and severity as well as perhaps helping investigators and clinicians to better understand the pathophysiology of this condition (Bach M et al. 2007).

The few initial papers reporting on PERG recordings in glaucoma patients showed a significant latency reduction with prolonged amplitude in glaucomatous eyes (May JG et al., 1982; Bobak P et al., 1983; Wanger P et al. 1983; Papst N et al., 1984; Wanger P et al., 1985). In a glaucoma patient, it is expected that the positive amplitude (P50) and negative (N95) component will be equally affected in PERG recording (Bach M et al., 1988). Viswanathan et al. (2000) in their study had reported a 60% and 23% reduction of the amplitude P50 and N95 responses respectively.

However, Hood et al. (2005) reported there were overlaps of controls and patients' P50 and N95 responses, while more pronounced changes observed in latency of P50-N95 and index ratio of N95/P50 for glaucoma patients. The variable response in their study was found to be influenced by the wide distribution of disease severity as well as the difference in PERG recording strategy used.

The knowledge on PERG in glaucoma had been further expanded in a study by Parisi V et al. (2006) who studied the response of PERG in patients with glaucoma and ocular hypertension (OHT). In that study, they reported significant changes in both the latency of P50 and amplitude of N95 in POAG and OHT patients as compared to normal patients. The study also reported a significant correlation of PERG with visual field defect based on Humphrey's visual field analyser (HFA). The glaucomatous visual field defect was reported based on the mean diffrent (MD (dB)) in that study. At the end of their study, they had concluded that PERG had a potential diagnostic ability to diagnose early stage of glaucoma, although there was no visual field defect in patients with clinically evident glaucomatous optic disc changes. Bach M et al. (2007) reported that appropriate recording techniques and paradigms of PERG had a sensitivity and specificity of more than 70% in detecting early glaucoma and had a potential to identify eyes at risk a year earlier before the field damage manifest.

However, PERG is still not routinely used in daily clinical practice in managing glaucoma patients. It requires rigorous and standardised recording techniques plus experienced and trained operators to achieve reliable and reproducible results (Bach M et al., 2007). Efforts are being undertaken to address these issues. The International Society for Clinical Electrophysiology of Vision (ISCEV) had, in 2012, published a guideline on PERG. Other electrophysiological test such as multifocal ERG and multifocal PERG together with reporting PERG based on index amplitude and latency of small to large check are now being extensively studied (Bach M et al., 2013; Roa A 2014).

1.7 Pattern Visual Evoked Potential (PVEP) in Glaucoma.

Visual evoked potential (VEP) response is generated by an electrical potential gradient recorded between the scalp and the eye in response to light (flash VEP) or pattern stimulation (PVEP). PVEP has the ability to detect functional visual integrity within the visual pathway from inner retina layer to the visual cortex (retino-cortical response); however, it is less useful in postchiasmatic disorders (Celesia GG et al., 1993; Odom JV et al., 2004; Odom JV et al., 2010). PVEP is the most preferred test in clinical disease due to its relatively low variability of waveform & peak latency both within a subject and over the normal population.

Odom JV et al. (2010) had established ISCEV latest guideline (2009) to perform standard method of recording PVEP. The guidelines provide comprehensive instructions in eliminating non-pathophysiologic parameters such as pattern size, pattern contrast, mean luminance, signal

filtering, patient age, refractive error, poor fixation, and miosis in recording PVEP as the reading will be affected. The pattern reversal VEP consists of a prominent positive component at approximately 100ms (P100) preceded and followed by negative components, N75 and N135 (Holder GE, 2004).

Several studies have reported on alterations in PVEP recording with reduced response observed in glaucomatous eyes (Marx MS et al., 1987; Falsini B et al., 1991; Parisi V et al. 1997). The results obtained were described as consequences of the dysfunction of the innermost retinal layers resulting in impairment of neural conduction in the optic nerve and in the whole postretinal visual pathways (Marx MS et al., 1987; Falsini B et al., 1991; Parisi V et al. 1997; Odom JV et al., 2010). Two previous animal studies by Dandona L et al. (1991) and Weber AJ et al. (2000) in which glaucoma had been induced demonstrated abnormalities both histologically and functionally involving the lateral geniculate nucleus. Subsequently Parisi V et al. (2001) reported a functional derangement in glaucoma can be demonstrated by PERG. This had include a reduced in PERG response resulting from the reduction in the magnitude and delayed timing of the input to the visual cortex.

To our best knowledge, there is limited study available reporting on PVEP response in PACG patients. Mitchell KW et al. (1989) had conducted a study on PVEP response specifically on 29 patients' eyes with history of acute angle closure. The study had reported an increased response in P100 in PACG patients compared to normal, while the PVEP amplitude demonstrated a delayed response. Another study done by Parisi v et al. (2006), also studied the PVEP parameters response in glaucoma, but their study samples were POAG and OHT patients.

They had reported significant reduction in all of the PVEP parameters response (including P100) in both groups, which is in contrast to PACG patients' response as outlined by Mitchell KW et al. (1989). Perhaps further longitudinal study involving the subgroups of glaucoma will enable us to see more consistent and established PVEP response in this disease.

1.8 Rationale of this study

Optic neuropathy is the main criteria to distinguish a PACG from primary angle closure. Once PACG is diagnosed, the risk of blindness is relatively high, and thus a proper mode of monitoring is needed to prevent blindness. Structural monitoring with latest technology from either SD-OCT or HRT III has gained popularity between both clinicians and researchers, nevertheless with further functional monitoring of visual field defect by HFA has helped in terms of staging the disease as well as monitoring the optic neuropathy.

The structural-function monitoring in glaucoma however had been reported to have some highly variable discrepancies between them. The challenge is more towards the diagnosis of the early stages of PACG, its progression as well as severity. Visual electrophysiological tests, which has the ability to detect and monitor RGC function, changes in early impairment rather than only when it is lost. This can perhaps give added value in terms of those limitations and also to determine the visual prognosis in severe PACG patients.

This study focuses on the visual electrophysiological changes in PACG patient and to establish any correlation between it with the glaucoma severity based on overall RNFL thickness (OCT) as well as AGIS score from visual field defect. Perhaps this test can be a complimentary test to OCT and Humphrey visual field in managing PACG patients.

2.0. OBJECTIVE

2.1 General Objective

To investigate the relationship between the visual electrophysiology test with structural and functional status of PACG patients.

.

2.2 Specific Objectives

1. To compare pattern VEP changes between PACG patients and control group.
2. To compare pattern ERG changes between PACG patients and control group.
3. To compare mean RNFL thickness using OCT between PACG patients and control group.
4. To determine the correlation between PVEP and PERG measurements with RNFL thickness in PACG patients
5. To determine the correlation between PVEP and PERG measurements with AGIS score in PACG patients.

2.3 Research questions

1. Is there any difference between PVEP measurement in PACG patients compared to control group?
2. Is there any difference between PVEP measurements in PACG patients compared to control group?
3. Is there any difference between RNFL analysis in PACG patients compared to control group?
4. Is there a correlation between PVEP and PERG changes with RNFL thickness in PACG?
5. Is there a correlation between PVEP and PERG changes with AGIS score in PACG?

3.0 METHODOLOGY

3.1 Research Design:

A case control study was the research design for this study.

3.2 Population, Place and period of study:

3.2.1 Study population:

PACG patients who attended the glaucoma clinic at Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian.

3.2.2 Place of study:

Ophthalmology Clinic, HUSM

3.2.3 Duration of Study:

This study was carried out for from June 2012 until May 2014. (2 years)

3.3 Sampling Method:

3.3.1 Selection Criteria:

Convenient sampling was applied on PACG patients under HUSM eye clinic follow up who fulfilled the criteria of this study.

3.3.2 PACG Group Inclusion Criteria

- Age more than 40 years old
- Patient diagnosed with Primary Angle Closure Glaucoma (PACG) based on gonioscopy finding and evidence of glaucomatous optic neuropathy from RNFL thickness defect (OCT) and Humphrey's visual field (HVF), with or without history of acute attack.
- Availability of two reliable, reproducible (HVF) test SITA standard 24-2.
- Availability of OCT image with signal strength more than 6/10.
- Patient who understand the nature of study and willing to sign the informed consent form.

3.3.3 PACG Group Exclusion Criteria

- Primary angle closure, primary angle closure suspect and all secondary angle closure glaucoma.
- History suggestive optic neuropathy and optic disc abnormality other than glaucoma.
- Glaucoma patients with concurrent other pre-existing retinopathy
- Patient who had previous post pan retina photocoagulation or retina surgery.
- Patient with impaired media opacity including cornea scar, significant cataract and vitreous hemorrhage that effected quality of OCT image.
- Pervious cerebral vascular accident (CVA) or intracranial lesion.
- Refractive error more than -5D or whose axial length more than 25mm.
- Refractive error more than +3D or whose axial length less than 21mm.

3.3.4 Control Group Inclusion Criteria

- Age more than 40 years old.
- Subjects who has normal ophthalmic examination and normal visual field.
- Intraocular pressure below 21mmHg.
- Goniscopy grade IV all quadrants.
- AGIS score of 0 from two reliable, reproducible (HVF) test SITA standard 24-2.
- Availability of OCT image with signal strength more than 6/10.
- Patient who understand the nature of study and willing to sign the informed consent form.

3.3.5 Control Group Exclusion Criteria

- Family history of glaucoma.
- Glaucoma suspects patients.
- Patient on prolonged steroid therapy.
- History suggestive optic neuropathy and optic disc abnormality.
- History of ocular trauma.
- Myopic more than -5D or whose axial length more than 25mm.
- Previous cerebral vascular accident (CVA) or intracranial lesion.
- Impaired media opacity including cornea scar, significant cataract and vitreous hemorrhage.

3.4 Sample Size Estimation

Sample size calculation determined by using PS (power and sample size) Software 2010. The calculation is done base on t-test, 2 mean (independent). Sample size done was base on each specific objective.

1) To determine PVEP parameters in PACG patients and Control:

Confident interval (C.I) $\alpha = 0.05$, study power (β) = 0.8 (80%), detectable difference between affected patient and unaffected patient (δ) = 3.0, Standard deviation (σ) = 3.7 (Keith w Mitchell at el 1989) and ratio PACG : control (1:1), M=1. n=25, total sample needed (n+10% drop out) will be 28 samples.

2) To determine PERG parameters in PACG patient and Control:

Confident interval (C.I) $\alpha = 0.05$, study power (β) = 0.8 (80%), detectable difference between affected patient and unaffected patient (δ) = 0.3, Standard deviation (σ) = 0.4 (Rachel at el 2009) and ratio PACG: control (1:1),M=1.n=29, total sample needed (n+10% drop out) will be 32 samples.

3) To determine RNFL analysis in PACG patients and Control:

Confident interval (C.I) $\alpha = 0.05$, study power (β) = 0.8 (80%), detectable difference between affected patient and unaffected patient (δ) = 5.1, Standard deviation (σ) = 6.9 (Hsin-Yi Chen et al 2011) Ratio PACG: control (1:1), M=1 n=30, total sample needed (n+10% drop out) will be 33 samples.

For our fourth and fifth specific objectives; correlation electrophysiology test with RNFL analysis, and AGIS score, to our best knowledge there were limited previous study done. The sample size calculation was based on above calculation. Since the largest sample obtained was 33 samples, we had decided to recruit 33 samples on each arm for each of our specific objective.

3.5 Definition of Terms.

a) The Primary Angle Closure Glaucoma (PACG)

The Primary Angle Closure Glaucoma (PACG) criteria are based on consensus of International Society Geographical & Epidemiological Ophthalmology (ISGEO) definition. (Foster *et al.,* 2002) which stated an eye with an occludable drainage angle and features indicating that trabecular obstruction by ≥270° of the peripheral iris has occurred, such as peripheral anterior synechiae, elevated intraocular pressure, iris whorling (distortion of the radially orientated iris fibres), "glaucomfleken" lens opacities, or excessive pigment deposition on the trabecular surface with presence of glaucomatous optic disc and visual field damage.