EVALUATION OF VISUAL ELECTROPHYSIOLOGY AND RETINAL NERVE FIBER LAYER ANALYSIS IN NONARTERITIC ANTERIOR ISCHAEMIC OPTIC NEUROPATHY PATIENTS

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DISCLAIMER

I hereby declare that work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged by in citation references.

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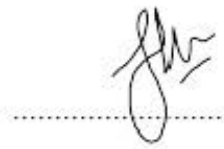

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LIST OF ABREVIATIONS

HUSM	Hospital Universiti Sains Malaysia
HVF	Humphrey Visual Field
IONDT	Ischaemic Optic Nerve Decompression Trial
IOP	Intraocular Pressure
ISCEV	International Society of Clinical Electrophysiology of Vision
MD	Mean Deviation
NAION	Nonarteritic Anterior Ischaemic Optic Neuropathy
OCT	Ocular Coherence Tomography
OHT	Ocular Hypertension
ONH	Optic Nerve Head
PERG	Pattern Electroretinogram
PSD	Pattern Standard Deviation
PVEP	Pattern Visual Evoked Potential
RAPD	Relative Afferent Pupillary Defect
RGC	Retinal Ganglion Cell
RNFL	Retina Nerve Fibre Layer
VA	Visual Acuity

ABSTRAK

PENGENALAN

'Nonarteritic Anterior Ischaemic Optic Neuropathy' (NAION) adalah penyakit di kalangan orang yang berusia 50 tahun dan ke atas yang menyebabkan kebutaan kekal. Penilaian dan pemantauan penyakit ini perlu untuk menilai kerosakan dari segi struktur dan fungsi saraf mata. Ujian Electrophysiology penglihatan (pattern electroretinogram (PERG) dan pattern visual evoked potential (PVEP)) berkebolehan mengesan degeneratif saraf 'axon' dan 'retina ganglion cells (RGC)' di dalam pesakit ini. Penilaian struktur lapisan fiber saraf retina (RNFL) dengan menggunakan ujian 'Optical Coherence Tomography' (OCT) menghasilkan imej RNFL secara 3 dimensi, membuat penilaian ketebalan RNFL secara objektif dan dapat mengesan kerosakan struktur. Ia merupakan ujian pelengkap kepada ujian struktur dan fungsi saraf mata.

OBJEKTIF

Pengkajian keatas maklumbalas ujian electrophysiology penglihatan dan lapisan fiber saraf retina (RNFL) dalam pesakit NAION. Korilasi di antara ujian elektrofisiologi penglihatan dengan ketebalan RNFL turut dikaji.

METODOLOGI DAN BAHAN

Satu kajian perbandingan hirisan lintang telah dijalankan di Hospital Universiti Sains Malaysia melibatkan 42 orang subjek daripada pesakit NAION dan normal. Pemeriksaan lengkap dijalankan bagi pengesahan penyakit NAION. Ujian struktur RNFL dilakukan menggunakan Cirrus SD-OCT (Carl Zeiss Meditec Inc, USA) dengan kekuatan penunjuk yang bagus ($\geq$ 6/10), manakala PERG (size 'checks'0.8º) dan PVEP (size 'checks'0.25º) dilakukan oleh juru teknik yang terlatih. Analisa statistik dilakukan dengan menggunakan ujian 'Mann-Whitney' dan 'Spearman's correlation coefficient'.

KEPUTUSAN

Terdapat signifikasi statistik pengurangan ‘amplitude’ dan pemanjangan tempoh ‘latency’ PVEP dalam pesakit NAION ($p<0.001$). Terdapat juga signifikasi statistik pengurangan pada ‘amplitude’ ($p<0.001$) dan pemanjangan tempoh ‘latency’ ($p<0.001$) PERG. Terdapat signifikasi statistik pengurangan ketebalan RNFL secara keseluruhan dalam pesakit NAION ($p<0.001$). Ketebalan RNFL menunjukkan tiada signifikasi statistik dengan ‘latency’ dan ‘amplitude’ PVEP dan PERG.

KESIMPULAN

Electrophysiology penglihatan dan analisis RNFL menunjukkan perubahan yang signifikasi tehadap para pesakit NAION. Hal ini menyokong yang PERG, PEVP dan OCT merupakan ujian komplimentari untuk penilaian dan pemantauan perubahan pada fungsi dan struktur saraf mata dalam pesakit NAION.

KATA KUNCI

‘Nonarteritic anterior ischaemic optic neuropathy (NAION)’, pattern electroretinogram (PERG), pattern visual evoked potential (PVEP), lapisan fiber saraf retina (RNFL).

ABSTRACT

INTRODUCTION

Nonarteritic anterior ischaemic optic neuropathy (NAION) is a disease among elderly more than 50 years old that leading to blindness. Assessment and monitoring of this disease is essential in order to evaluate the structural and functional damage. Visual electrophysiology tests (pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP)) able to detect axonal degeneration and functional impairment of retina ganglion cells (RGC) in patient with NAION. Assessment of Retinal Nerve Fiber Layer (RNFL) with Optical Coherence Tomography (OCT) provides 3-Dimensional image of RNFL, objectively evaluate the RNFL thickness and detection of structural damage. It compliments the existing standard structural and functional test.

OBJECTIVE

To evaluate visual electrophysiology response and retina nerve fibers layer (RNFL) thickness in NAION. The correlation between visual electrophysiology with RNFL thickness were also evaluated.

MATERIALS AND METHODS

A comparative cross sectional study was conducted in Hospital Universiti Sains Malaysia involving 42 samples of NAION patients and controls. A complete ocular examination was done to confirm the diagnosis of NAION. Evaluation of structural changes of RNFL was conducted using Cirrus SD-OCT (Carl Zeiss Meditec Inc, USA) with good signal strength (≥ 6/10). PERG (0.8º checks size) and PVEP (0.25º checks size) was conducted by a trained technician. Mann-Whitney test and Spearman's correlation coefficient analysis were used in statistical analysis.

RESULTS

There were statistically significant reduction in amplitudes and prolonged in latencies of PVEP in NAION patients ($p<0.001$). There were also significant reduction in magnitude of amplitude ($p<0.001$) and prolonged latency in PERG ($p<0.001$). There was also significant thinning of Mean RNFL thickness in NAION patients ($p<0.001$). No significant correlation between RNFL and latency and amplitudes of PVEP and PERG.

CONCLUSION

Visual electrophysiology tests and RNFL analysis has shown significant changes in NAION patients. This supports that PERG, PVEP and OCT are complimentary tests in assessment and monitoring structural and functional damage in NAION.

KEY WORDS

'Nonarteritic anterior ischaemic optic neuropathy (NAION)', pattern electroretinogram (PERG), pattern visual evoked potential (PVEP), retina nerve fiber layer (RNFL).

Chapter 1

INTRODUCTION

Introduction.

1.1 Nonarteritic anterior ischaemic optic neuropathy (NAION).

Nonarteritic anterior ischaemic optic neuropathy (NAION) is the most common type of ischaemic optic neuropathy. This condition ultimately lead to permanent visual loss in middle-aged and elderly population. It can be defined as acute optic nerve ischaemia due to microcirculatory embarrassment. This lead to disturbance of perfusion to the proximal portion of the optic nerve supplied by the posterior ciliary artery. Nonarteritic implies to the condition whereby the ischaemia does not attributed from vasculitis in which commonly due to giant cell arteritis. Hayreh (1974) defined “anterior” to denote optic nerve head swelling in acute phase compared to rarer posterior type with normal disc appearance. Although the condition classically occurred in patients age 50 years and older, the age group shifted towards younger age group in patient with Diabetes Mellitus and Hypertension. (Repka MX et al., 1983).

Limited data reported on the incidence of NAION in other countries apart from United States. One study reported about the incidence of NAION in Asian country in Beijing done by Xu L et.al (2007), the annual incidence in Chinese population approximately 6.25 per 100,000. The incidence is higher in United States and this is comparable to commoner disease among Caucasians (Lee MS et al., 2011; Johnson LN and Arnold AC, 1994).

Classically, patients presented with acute onset of painless unilateral loss of vision or field defect. The vision loss commonly take place upon awakening and describe as diffuse blurring or cloudiness of vision. If they have field defect, typically it involved inferiorly which

classically describe as altitudinal field defect. (Hayreh SS and Zimmerman B, 2005). Visual acuity can be vary, ranging from 20/15 to as worse as no light perception. Surprisingly, in a study done by Hayreh SS and Zimmerman MB (2008), a normal or near normal visual acuity during presentation found in 50% of patients. Thus, NAION cannot be overlook in patient with good visual acuity. Patients also have colour vision defect in keeping with the degree of visual acuity loss.

In unilateral case, a relative afferent pupillary defect is always present. Small number of patient will experience eye pain or discomfort and pain on eye movement that typically a feature of optic neuritis is absent in NAION, thus can discriminate between these two disease conditions. (Swartz Ng et al., 1995).

Fundus examination in NAION reveals optic disc swelling either diffuse or segmental with peripapillary flame shape hemorrhage. The unaffected contraleral eye usually will have small or absent physiology cup, describe as “disc at risk” (Miller NR, 2011 and Atkins EJ et al., 2010). Hayreh SS and Zimmerman MB came out with a new disease entity describe as “incipient NAION” and has been occurred in higher number of cases in diabetic patients. In these cases, patients experienced disc edema but asymptomatic. Then it resolves and recur symptomatically in 25% of patient.

1.2 Pathogenesis of NAION.

Pathogenesis of NAION is still unknown. It postulated as a result of microcirculatory insufficiency at the level of the optic nerve head blood supply. Many studies regarding the aetiology of NAION focused on Short Posterior Ciliary Arteries (SPCA) and choroidal circulation and factors that affecting this vessel. Knox DL et al (2000) from histopathology evidence documented infarction of the optic nerve head. Oliver JM et al (1990) and Onda E et al (1995) in their autopsy eye demonstrated that the optic disc is supplied by partial or complete vascular circle derived from the SPCAs. This vascular circle may have distinct upper and lower halves division which consistent with altitudinal damage if it is affected. Fluorescein angiography further defined this location of vessels that compromise in NAION. Hayreh SS (1990) found delayed in filling of prelaminar optic disc from Fluorescein Angiography while Arnorld AC and Hepler RS (1994) suggest that the level of vascular occlusion lies within the paraoptic branches of the SPCAs. Recent study using current technology further supported this evidence. Leiba H et al (2000) found decreased in optic nerve head blood flow measured by Laser Doppler flow study.

Several risk factors were identified that attributed to reduction on optic nerve head perfusion in NAION. Several studies have shown that systemic disease like Hypertension and Diabetes Mellitus have been associated with NAION. (Boghen DR and Glaser JS., 1975; Repka MX et al., 1983; Hayreh SS et al., 1994; Ischaemic Optic Neuropathy Decompression Trial Study Group, 1996). Jacobson DM et al (1997) found smoking and hypercholesterolemia as another risk factors.

Structure of the optic disc play a role in NAION. The discs in patients with NAION are often small in diameter and small or absent in cups suggesting ‘crowding’ disc may impart in pathogenesis of this disease. This crowding postulated that it will cause mechanical obstruction to axoplasmic flow, thus produces intracellular axonal swelling and compromise microcirculation in that crowded region. Another possibilities is secondary obstruction to axoplasmic flow occurs after acute ischaemia will result in ganglion cell death. (Feit RH et al., 1984; Doro S and Lessell S, 1985; Beck RW et al., 1987)

Apart from mechanical factors, Hayreh SS et al (1994) has postulated that nocturnal hypotension may impart in pathogenesis of NAION. He stated that hypotension that normally occurs during sleeping may compromise optic disc circulation, in particular in patients with systemic hypertension where exaggeration of nocturnal drop in blood pressure occurs. It further aggravated by aggressive treatment with antihypertensive medication that administered at night. Landau K et al (1996) in contrast found that slower rise in mean blood pressure in early morning in patients with NAION.

Hayreh SS et al (1999) in his study found that impairment in the normal autoregulatory mechanism that control the blood flow in the optic nerve vasculature play a role in the pathogenesis. In his study, he found that impairment of this autoregulation as a result of endogenous serotonin released within atherosclerotic plaque and also mediated by endhothelin that both results in arterioles vasoconstriction.

1.3 Treatment and Management of NAION.

Management of NAION is still questionable and several therapies have been used but none of the treatment applied has been shown to be effective. Management dilemma surrounding this disease are no establish treatment in acute NAION and no preventive treatment for a subsequent attack on the fellow eye which estimated to be 15%-25%. (Kuppersmith MJ et al., 1997). Wide range of treatment in NAION presumed to act on thrombosis, on the blood vessels, on reduction of disk edema in acute stage which will ameliorate damage and preserved vision, and few treatment presumed to have a neuroprotective effect.

Ischaemic Optic Neuropathy Decompression Trial (IONDT) compared the visual outcomes of patients observed without treatment with those of patients treated with optic nerve fenestration. Patient undergone optic nerve fenestration showed improvement of three lines of visual acuity in earlier study (IONDT. 1996). However recent IONDT (2000) clinical trials evaluated this surgical modality have shown that no differences in visual outcome compared to untreated group and patient undergone optic nerve fenestration have experienced more deterioration in visual acuity.

Corticosteroid has been used as primary medications, either systemic steroid or intravitreal injection of triamcinolone to reduce the disc edema in acute stage. Improvement of visual acuity has seen in steroid-treated group as compared to untreated in several studies. (Hayreh

SS and Zimmerman MB, 2008; Hayreh and Zimmerman, 2007; Hayerh 2008; Hayreh 1974). However, this studies done in a very small group of patient and larger sample size encouraged in future study.

Several therapies have been proposed including anticoagulation, aspirin, sub Tenon injections of vasodilators, intraocular pressure lowering agents such as brimonidine, thrombolytic agents and hyperbaric oxygen. (Ellenberger C Jr et al., 1974; Kollarits CR et al., 1981; Batelho PJ et al., 1996; Arnold Ac et al., 1996; Fazzone HE et al., 2003). Unfortunately none of this therapy has been proved to be effective.

Although no validate treatment in NAION, optimisation of medical conditions such as Diabetes Mellitus, Hypertension and Hypercholesterolemia is important in prevention of the attack on the fellow eye. (Newman NJ et al., 2002). Although smoking has a weak correlation with NAION, it is advisable to stop smoking to prevent cardiovascular disease. (Hayreh SS et al., 2007). Furthermore, patients in whom NAION developed are at risk for developing cerebrovascular and cardiovascular events such as transient ischaemic attack, stroke and myocardial infarction.

1.4 Pattern Visual Evoked Potential (PVEP) in NAION.

Visual Evoked Potential (VEP) is a cortical response generated by an electrical potential gradient recorded clinically by placing wire electrodes adjacent to the occipital cortex and to a non-visual area of the brain. It reflects the patency of visual pathway and to assess optic nerve function and its projection to the visual cortex. In PVEP, the stimulus used to generate the wave is an alternating high contrast checkerboard. The responses stimulate by this stimuli have less intra- and inter-individual variability and much sensitivity and accuracy in detecting minor visual pathway abnormality compare to Flash VEP and the most preferred test in clinical disease. (American Clinical Neurophysiology Society. Guideline 9B: Guidelines on visual evoked potentials. 2006).

ISCEV latest guidelines on standard method of performing and recording PVEP provide comprehensive instructions in eliminating errors. Non-pathophysiologic parameters that affect the PVEP reading such as pattern size, pattern contrast, mean luminance, signal filtering, patient age, refractive error, poor fixation, and miosis were considered during performing PVEP (Odom JV et al., 2010). Prolongation of P100 latency measured in PVEP considered the most reliable parameter in detecting clinical abnormality. It less affected by degree of patient cooperation and technical factors. (American Clinical Neurophysiology Society. Guideline 9B: Guidelines on visual evoked potentials. 2006).

Several studies reported on abnormality in PVEP recording in NAION patients. (Wilson WB 1978; Janaky M et al., 2006; Atilia H et al., 2006, Parisi V et al., 2008). Variations in PVEP findings reported in their study. The initial study by Wilson WB (1978) found that severe reduction in amplitude with little or no change in latency. In contrast to more recent study by

Janaky M et al (2006) found prolongation in latency as well as reduction in amplitude. Interestingly, in this study they found abnormal changes in VEP in terms of waves and latency of the fellow unaffected eye suggested early detection of involvement of the fellow eye. However further longitudinal study and bigger sample size needed to evaluate this findings.

Few animal studies conducted this electrophysiological evaluation for further understanding of pathogenesis of this disease. (Chen CS., 2008; Chuman H, 2014; Bernstein SL., 2011). Berstein SL (2011) and Chen CS (2008) found similar findings of reduction in amplitude but normal in latency in their animal models of NAION. The VEP amplitude depression persistent in animal study showed that permanent degradation of optic nerve electrical activity. Chuman H (2014) further evaluate the use of PVEP in the treatment of NAION. As the results of animals study comparable to the human eye with NAION, this provide further understanding of the human axonal damage after axonal ischaemia.

1.5 Pattern Electroretinogram (PERG) and NAION.

In NAION, circulatory insufficiency within the optic nerve head presumed to be a cause although specific mechanism remains elusive. Although PERG is a good tool of assessment, the role of PERG is still minimal in assisting management of NAION. With PERG, it helps in objectively evaluate functional deficit of patient and further understanding of pathogenesis of the disease. The measurements will convey regarding the actual site of involvement, whether it confined to the optic nerve or other layers of retina would also involve. Besides estimation of visual acuity and visual field, it contribution will demonstrate the extent of visual deterioration of patient, thus will aid in prognosis.

To better understanding regarding the role of PERG in NAION, review of histopathologic evidence are reported by animal and human study. In primate-induced NAION model by Chen CS et al (2008), histopathologic evidence showed reduction of number of cells in the ganglion cell layer, axonal disruption and thinning of RNFL. This will give rise to reduction of PERG N95 amplitude selectively as N95 is generated in relation to retina ganglion cell function. This study supported by another animal study done by Chuman et al (2012), in rodent-induced NAION showed similar findings of loss of RGC however electrophysiological study in this rodent did not found any significant changes in PERG. Comparable to human study by Levin LA and Louhab A (1996), reported a case of evidence of human RGC apoptosis in NAION. The rate of RGC death in human is questionable, but it takes 2 to 12 weeks based on monkey study (Quigley HA et al., 1995). Atilia H et al (2006) found a difference in her study whereby retrograde degeneration occurred on the RGC axons as a result of compromise to the optic nerve or direct damage to the RGC bodies.

Electrophysiological studies done in NAION patients still limited. Only few papers reporting on PERG recordings in NAION patients. Parisi et al (2008) found reduction in amplitudes as well as delayed implicit times. Comparable to this study, Janaky M et al (2006) and Atilia H et al (2006) found decreased in N95 amplitude but no difference in latency. Froehlich J and Kaufman DI (1994) done a study in acute stage of NAION showed similar findings of reduction in N95 amplitude. Janaky M et al (2006), Atilia H et al (2006) and Froehlich J and Kaufman DI (1994) found similar findings in their study that P50 amplitude and latency was normal. This would explain that P50 usually affected by dysfunction of the macula which the wave arise largely from macular photoreceptors. In contrast, Parisi et al (2008) found delayed in P50 latency. This variable response was found to be influenced by the difference in disease severity and in PERG recording strategy used.

The knowledge on the PERG in NAION had been further expanded in a study done by Froehlich J and Kaufman DI (1994) who studied the response of PERG in patients with NAION and Optic Neuritis. In that study, they reported a reduction in N95 amplitude with no change in patients with optic neuritis in early course of the disease. This findings had concluded that PERG had a potential diagnostic ability to diagnose NAION if the judgement of making diagnosis is equivocal especially in younger patient without medical comorbidities. More studies require to further evaluate and support this findings for future use.

However, PERG is still not routinely used in daily clinical practice. It requires demanding and standardised recording technique 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 are now emerged and being extensively studied. Reporting PERG based on index amplitude and latency of small to large checks are now widely considered. (Bach M et al., 2013).

1.6 Optical Coherence Tomography (OCT) in NAION.

Optical coherence tomography (OCT) has become an important tools for objective assessment and measurements of the optic nerve head and peripapillary retinal nerve fiber layer thickness (RNFLT). With emergence of this new technology, it becomes a complimentary tool to a clinical examination and fundus photography. The commonly used Cirrus HD-OCT, a spectral domain OCT device has offered a faster scan speed and a higher image resolution, providing high quality image for RNFL imaging. Thus, with this advantages, it provides superiority in terms of reproducibility and reliable measurement, its diagnostic capability and the strength between structure-function relationships. Besides 3-dimensional imaging of the RNFL, it has low measurement variability (Leung CK et al., 2009).

OCT allows direct measurement of RNFL thickness by in vivo visualisation of the retinal layers and anatomical changes. In patients with NAION, during the acute phase of ischaemic insult, there is acutely swelling of RNFL and thinning after 3 to 6 months which correlate with visual field loss. During this acute phase, the swelling of the RNFL will mask the effect of measuring axonal loss. Thus, analysis of ganglion cell layer at this stage showed significant thinning as compared to RNFL. This would indicate that measurements of RGC layer in OCT represents a biomarker of early structural loss in NAION. Maekubo T et al (2013), in their experimental study found that OCT images are analogous to histologic cross-sectional findings. This ganglion cell layer undergone axonal damage directly or as a result of retrograde degeneration following ischaemic insult. Similar to this study, Ho JK et al (2013) found that measurements of retinal layer changes using OCT is an equal to histologic findings

of retina ganglion cell axon loss. This concluded that this non-invasive method is equal to dissection of difference structure of retinal layers.

Apart from measurement of RNFL thickness in NAION, it allows objective analysis of optic nerve head parameters. This parameters are equally important to RNFL analysis since it is known in NAION patients that the disc area is small and small cup-to-disc ratio. This condition usually referred to as the “disc at risk”. Saito H et al (2006) and Danesh Meyer HV et al (2005) have confirmed this findings in patient with NAION. Comparable to this study done by Contreras et al (2007), patients with NAION have lower cup to disc ratio as compared to the normal population.

Variability in clinical presentations in term of visual field defects and optic disc pallor in NAION makes these two major diagnostic criteria need further evaluation. In contrast to objective evaluation of visual field defect with standard automated perimetry, assessment of optic disc pallor is highly dependent on clinicians. The extent and degree of pallor measurements can be influenced by many factors including media interference for example cataract or pseudophakic eye. Janaky M et al (2006) found that degree of optic disc pallor did not correlate well with visual acuity. This assessment could be subjective with high inter-individual variations. Thus, with OCT it helps in objectively measured the damage that has occurred to the retina nerve fiber layer after the ischaemia that aid in more accurate visual prognosis.

Apart from quantification of RNFL and optic nerve head measurements in further understanding pathogenesis of this disease, it also helps in identification of different pattern of RNFL involvement pertaining to visual field loss in NAION. Deleon-Ortega J et al (2006) showed that visual field mean deviation correlated better with OCT RNFL thickness. Thus, it correlate better structural and functional assessment. Additionally, it produced the information regarding the relationship between RNFL thickness and Visual Field (VF) sensitivity in a non-affected field. Chan CK et al (2009) showed that eyes affected by NAION had thinner RNFL than control eyes in regions that unaffected hemifield. This interesting finding suggests that measurement of RNFL with OCT would tell the extension of RNFL involved beyond the field measured with standard automated perimetry. This information has prospective in term of estimation of visual potential and for follow-up of patients.

1.7 Rationale of this study.

Clinical assessment of NAION using slit lamp biomicroscopy and fundus photography yield high inter-individual variability. Assessment of pallor of optic disc affected by media of the eye (e.g cataract or pseudophakic) and gives false impression about the real colour of the disc. In some measure, the degree of pallor does not really correlate well with visual acuity.

Hitopathologic study of an eye with NAION has shown loss of cells and their axons, thinning of RNFL and reduced number of Retinal Ganglion Cells (RGCs). Structural assessment of NAION with latest technology using OCT has gained popularity compliments conventional method of assessment of this disease. It produces 3-dimensional image of RNFL with low measurement variability. It is a non-invasive technique, provides objective evaluation of RNFL thickness and detection of structural loss in patient with NAION.

Functional assessment using electrophysiological tests such as PVEP and PERG aids in further characterisation of pathophysiology of the diseasethat still in questions. Measurement of P100 amplitude and latency in PVEP represents most of cortical response. In PERG, measurement of P50 and N95 amplitude and latency provides assessment of macula fibers and Retinal Ganglion Cells function respectively. This measurements will objectively evaluate the functional damage in NAION, compliments the structural evaluation.

The relationship between structural and functional alterations has never been thoroughly evaluated in NAION. This study focuses on the visual electrophysiological changes in NAION patients and to establish correlation between it with the overall RNFL thickness from the OCT. Perhaps this test can be a complimentary tests to conventional way of assessing and monitoring patient with NAION.

Chapter 2

OBJECTIVES

2.0 OBJECTIVE.

2.1 General Objective

To evaluate the relationship of RNFL thickness to electrophysiological changes in patient with NAION.

2.2 Specific Objectives

1. To compare PVEP changes in NAION patients with control group.
2. To compare PERG changes in NAION patients with control group.
3. To compare RNFL thickness in NAION patients with control group.
4. To determine the correlation between mean RNFL thickness and PVEP amplitude and latency in NAION patients.
5. To determine the correlation between mean RNFL thickness and PERG amplitude and latency in NAION patients.

2.3 Research questions.

1. Is there any difference between PVEP amplitude and latency measurements in NAION patients compared to control group?
2. Is there any difference between PERG amplitude and latency measurements in NAION patients compared to control group?
3. Is there any difference between RNFL analysis in NAION patients compared to control group?
4. Is there a correlation between mean RNFL thickness and PVEP amplitude and latency in patient with NAION?
5. Is there a correlation between mean RNFL thickness and PERG amplitude and latency in patient with NAION?

Chapter 3

MATERIALS &METHODS

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:

NAION patients who attended Neuroopthalmolgy clinic at Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian.

3.2.2 Place of study:

Ophthalmolgy Clinic, HUSM.

3.2.3 Duration of Study:

This study was carried out from June 2013 until November 2014.

3.3 Sampling method:

3.3.1 Selection Criteria:

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

3.3.2 NAION Group Inclusion Criteria

- Age more than 40 years old.
- Patient diagnosed with NAION based on history of unilateral acute vision loss, Positive Relative Afferent Pupillary Defect (RAPD), optic disc swelling and visual field defect.
- Confirmed case of NAION for minimum of 6 months.
- Patient who understand the nature of study and willing to sign the informed consent form.

3.3.3 NAION Group Exclusion criteria.

- Patient presented with other cause of optic neuropathy.
- Patient with optic disc abnormality.
- Presence retina pathology for example retinal detachment, maculopathy, panretina photocoagulation scar.
- Presence of media opacity including dense cataract, cornea opacity, vitreous haemorrhage that affected quality of OCT image.
- Patient diagnosed with glaucoma.
- Presence of intraocular inflammation for example anterior and posterior uveitis.
- Patient with trauma or ocular injury.
- Patient with high myopia of more than -5.00D 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 matched to study group.
- Subjects who has normal ophthalmic examination and normal visual field.
- Patient who understand the nature of study and willing to sign the informed consent form.

3.3.5 Control Group Exclusion Criteria.

- History suggestive of other causes of optic neuropathy and optic disc abnormality.
- History of ocular trauma.
- Glaucoma suspect patients.
- Impaired media opacity including cornea scar, significant cataract and vitreous hemorrhage.
- Previous cerebrovascular accident (CVA) or intracranial lesion.
- Myopic of more than -6.00D or whose axial length more than 25mm.
- Refractive error more than +3D or whose axial length less than 21mm.
- Impaired media opacity including cornea scar, significant cataract and vitreous haemorrhage.

3.4 Sample Size Estimation.

Sample size calculation determined by using PS (power and sample size) Software 2010. Sample size done was based on each specific objective.

1) **To determine PVEP parameters in NAION 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) = 8.0 (Parisi V et al 2008) Ratio NAION: control (1:1), M=1, n=19, total sample needed (n=10% drop out) will be 21 samples.

2) **To determine PVEP parameters in NAION 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) = 8.0 (Parisi V et al 2008) Ratio NAION: control (1:1), M=1, n=19, total sample needed (n=10% drop out) will be 21 samples.

3) **To determine RNFL analysis in NAION 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) = 53.0 (Bellusci C et al 2008) Ratio NAION: control (1:1), M=1, n=19, total sample needed (n=10% drop out) will be 21 samples.

For our fourth and fifth specific objectives; correlation electrophysiology test with RNFL analysis, 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 21 samples, we had decided to recruit 21 samples on each arm for each of our specific objective.

3.5 Definition of Terms.

a) The Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)

The diagnosis of NAION are based on clinical symptoms, signs and visual field defect. The ischemic optic neuropathy decompression trial (IONDT) clinical trials (1998) stated that patients with sudden onset of unilateral vision loss, with relative afferent pupillary defect (RAPD) positive, swollen optic disc and visual field defect are considered criteria to diagnose NAION. Apart from this, patients also has no symptoms or signs to suggest Giant Cell Arteritis (headache, pain at temporal area, tender and palpable thickened temporal artery with raised Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP)).

b) Relative afferent pupillary defect (RAPD)

It is elicited by swinging flashlight test to evaluate any optic nerve damage. This test is very useful for detecting NAION and can differentiate it with other disease for example diabetic papillitis. There is less pupillomotor stimulation reaching the brainstem when the light shines into the eye with NAION, thus diminished in pupillary response.

c) The retinal nerve fiber layer (RNFL) thickness

The retinal nerve fiber layer (RNFL) is formed by the radial expansion of the fibers of the optic nerve. Character of this structure around peripapillary area can facilitate optic neuropathies especially in glaucoma. Ocular Coherence Tomography (OCT) is a promising new modality that uses back reflected infrared light (820nm) to produce high resolution cross-sectional images of the RNFL. In evaluating a NAION patient, OCT generate optic nerve head (ONH) image includes in 3-dimentionals image and peripapillary retina nerve fiber layer (RNFL) parameters to detect thinning area affected by ischaemic insult. The Fast RNFL Thickness protocol on OCT was used to yield 3.4-mm-diameter circular scans for each eye. Presence of uniform signal intensity, strong reflectance signal from the RNFL (more than 6/10) and the retinal pigment epithelium resulting in clear demarcation of both layers without the absence of any part of image constituted a good-quality scan. The parameters calculated are average RNFL thickness, mapped in the four quadrants; superior, inferior, nasal, and temporal field area. Coloured coded green for normal, yellow for suspicious and red for damage RNFL. (Prashant Naithani et al., 2007).