INTERTONE LATENCY DIFFERENCE OF AUDITORY BRAINSTEM REFLEX IN PATIENT WITH ENDOLYMPHATIC HYDROPS

BY

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ABSTRAK

PERBEZAAN MASA KEPENDAMAN DI ANTARA GELOMBANG BUNYI OLEH

UJIAN ‘AUDITORY BRAINSTEM RESPONSE’ DI GOLONGAN PESAKIT

DENGAN KELEBIHAN KANDUNGAN CECAIR DI BAHAGIAN TELINGA DALAM ‘ENDOLYMPHATIC HYFROPS’.

Pengenalan: Idiophatic Endolymphatic hydrops (EH) juga dikenali sebagai penyakit Meniere (MD), adalah gangguan sistem vestibular yang jarang, disebabkan oleh ketidakseimbangan cecair endolymph dalam telinga. Ia menyebabkan pening (vertigo), kehilangan pendengaran sensorineural (SNHL), tinnitus dan ketidakselesaan telinga. ‘Auditory brainstem response ‘(ABR) adalah ujian neurologi menguji tindak balas batang otak terhadap rangsangan auditori. Perbezaan masa kependaman gelombang V (ITLD) boleh digunakan untuk mengukur masa transit bunyi dari frekuensi tinggi ke frekuensi rendah. Adalah dijangka masa transit lebih pendek untuk EH disebabkan kekakuan struktur telinga dalam.

Objektif: Kajian ini bertujuan untuk membuktikan ujian pendengaran (ITLD) sebagai alat diagnostik untuk masalah kelebihan kandungan cecair di bahagian telinga dalam. Kajian ini adalah untuk menentukan min (ITLD) ke atas pesakit yang mengalami kelebihan kandungan cecair di bahagian telinga dalam. Kajian ini juga menentukan korelasi antara ITLD dan ECoG untuk golongan pesakit EH.

Metodologi: Ia adalah kajian ‘cross-sectional’ dengan memilih pesakit dengan EH berdasarkan simptom klinikal dan ujian audiometri dijalankan. Empat belas pesakit menjalankan ujian ITLD

dan ECoG. Masa transit gelombang V pada frekuensi 500 Hz dan 4 kHz telah dikira. Nisbah (SP / AP) dalam ‘electrocochleograhy’ (ECoG) diukur.

Keputusan: Berdasarkan Mann-Whitney Test, min ITLD adalah tidak ketara untuk kekurangan pendengaran tahap ringan dan sederhana. Telinga kanan p-value = 0.699, telinga kiri p-value = 0.272. Berdasarkan Spearman’s Correlation Test, tiada korelasi antara ITLD dan ECoG. (telinga kanan p-value= 0.54, telinga kiri p-value= 0.794).

Kesimpulan: Ujian ITLD berperanan membantu mengenal pasti penyakit EH. Walau bagaimanapun, ia tidak menjadi alat diagnostik. Kajian juga membukti tiada perhubungan di antara ujian ITLD dan ECoG.

ABSTRACT

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Objectives: 1. To establish ITLD as a clinical diagnostic tool for EH. 2. To determine the mean of ITLD in patients with EH. 3. To determine the correlation between ITLD and electrocochleography (ECoG) in EH.

Methodology: It was a cross-sectional study by selecting patients with EH based on clinical symptoms and pure tone audiometry (PTA) results. Fourteen patients tested for ITLD and ECoG.

The travelling time of wave V at frequency 500 Hz and 4 kHz were calculated. The summation potential and action potential ratio (SP/AP) were measured.

Results: Based on Mann-Whitney test, it shown two median of ITLD is not significant for mild and moderate hearing loss (HL), right ear p-value = 0.699, left ear p-value = 0.272. Based on Spearman's Correlation test, there is a not significant correlation between SP/AP ratio and ITLD (right ear p-value= 0.54, left ear p-value= 0.794) among the participants.

Conclusion: Since there was no correlation between ITLD and ECoG. ITLD is important assisting to identify EH, however it might not be useful as a diagnostic tool.

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

Endolymphatic hydrops (EH) is a disorder of the vestibular system of the inner ear consists of abnormal fluctuations in the endolymph fluid which fills the membranous labyrinth. The overproduction or malabsorption of endolymph causes an abnormal increased volume of endolymph in cochlear, resulting in gross enlargement or distension of membranous labyrinth. The primary idiopathic EH is known as Meniere's disease (MD).

Meniere's disease is a disorder characterised by spontaneous attack of vertigo, fluctuating sensorineural hearing loss (SNHL) particularly at low frequency, tinnitus, aural fullness and associated with nausea and vomiting. These symptoms are recurrent & episodic, increase in intensity for minutes then lasted from several hours to days. The disease is often unilateral. There is no gender predilection. The onset is between 20-50 years old (commonest at 4th decade of life). There are many predisposing factors been ruled out such as genetic (14-20% are autosomal dominant), anatomical variant (e.g. small vestibular aqueduct), trauma, infection (eg. syphilis, mumps), allergy, autoimmunity, psychosomatic and personality features.

American academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [1] had published three categories of diagnosis: Definite MD: 2 or more spontaneous attacks of vertigo (20minutes or longer), hearing loss documented by pure tone audiogram at least 1 occasion, tinnitus or aural fullness at affected site. Other possible causes excluded. Probable MD: 2 or more spontaneous attacks of vertigo with unilateral hearing loss, tinnitus and aural fullness all at the same time. Possible MD: 2 or more spontaneous attacks of vertigo, no auditory symptoms during attacks (a temporary auditory disturbance not noticed by patient or the auditory symptoms happen later).

The pathophysiology of EH first related to regulation of endolymph volume and composition. A disturbance of ion transport system at inner ear could contribute to volume disturbance. The different ionic compositions and the different concentration gradient of electrical potential, this is important in regulating electrochemical impulses of hair cells. The cochlear haemostasis is related to the osmotic gradients and hormonal regulation. There are many hormonal mechanisms been suggested including β -adrenergic, muscarinic and purinergic receptors as [2]. The concentration of K+ ion is higher in endolymph than perilymph (endolymph 150 mM, perilymph 4-5 mM). If there is any alteration in transport of both K+ and counter ion (e.g. Cl- or HCO3-), this will allow accumulation of electrolyte in endolymph resulting in an osmotic influx of water. Aquaporins is a protein transporter which plays a role in water equilibration across the endolymphatic boundaries possibly part of the hormonal regulation. The osmolarity in endolymph is slightly higher (315 mosm/l) than perilymph (290 mosm/l) but the potential in endolymph is high due to its high ionic concentration. The body movements (fluid inertia) will affect the pressure fluctuation which driving the endolymphatic movements. Secondly, the inner ear pressure gradient plays a major role in EH. Both acute EH and the early phase of chronic hydrops occur with a change in pressure between endolymph and perilymph even as small as less than 0.5 mm Hg [3]. The endolymphatic boundaries are very compliant, even a very small pressure changes causes an increase in endolymph volume. This explains the bowing of Reissner's membrane in EH. Perilymphatic pressure is not elevated in the EH; only the endolymphatic pressure is elevated and this can influence the blood flow.

To diagnose MD in clinical practice is a challenging task. A baseline pure tone audiogram (PTA) is mandatory, serial PTA is useful in post treatment. Imaging studies, vestibular evoked myogenic potentials (VEMP), caloric test, posturography and glycerol test had been proposed as

important investigation for EH but they are not specific enough. Electrocochleography (ECoG) is established as a gold standard hearing assessment for MD. The endolymphatic pressure is elevated causing bowing of Reissner's membrane of cochlear due to endolymphatic distension. There is a nonlinear response in Reissner's membrane causing the summating potential (SP) increase. It measures the ratio of SP to action potential (AP) with a ratio greater than 0.4 is considered an abnormal result [27]. The sensitivity of ECoG in diagnosing EH is variable and its clinical application is still limited.

Auditory Brainstem Response (ABR) is an objective test used clinically in diagnosing patient with EH. The ABR represents initiated activity beginning at the base of the cochlea moving toward apex. The parameters of ABR such as absolute latencies, inter-peak latencies and inter-aural latencies differences have been established clinically to differentiate the types and degrees of hearing loss. Inter-tone latency measurements are used widely at audiology clinic. These measurements have potential to diagnose different types of SNHL such as presbycusis, MD and noise-induced hearing loss (NIHL). Interpretation of travelling wave time and motion can provide qualitative and quantitative information regarding the function of the auditory nerve or brainstem pathologies. It may discriminate MD from retrocochlear pathology as MD may mimic retrocochlear lesion and central lesion in clinical symptoms.

It has been established that the travel time and distance for a particular frequency component to reach its characteristic place (CP) within the cochlea is much longer for low frequencies than for high frequencies. The velocity of this travelling wave is very fast at the base, nearly instantaneous for frequency above 4 kHz (in the range of tens to hundreds of microseconds). However, the velocity of travelling wave at the apex noted slow down dramatically. The transmit time from base to apex required 10 ms or greater in normal hearing.

In EH, the stiffness at apex of cochlear is reduced. The changes of stiffness of the basement membrane in cochlear causes increase velocity of cochlear travelling wave. In MD, the latency delay in wave V is abnormally short. This mean an increase in the cochlear traveling wave velocity in patients with MD. Besides, in EH there is an excessive fluid in inner ear causing cochlear swelling. It present as a distension of Reissner's membrane into scala vestibule. There is also bounding of the saccule, utricle and ampullae of the semi-circular canals (SCC). A displacement of the basilar membrane in the apex of the cochlea is reported. The fluid will increase the solidity in inner ear, causing the sound to travel faster. Thus the cochlear traveling time from base to apex (high to low frequency) is expected to be shorter. Wave V pattern is significant on ABR recording thus easier to be recognized. In severe hearing loss > 70dB, there are recruitment in cochlear hair cells resulting in normal ITLD. Thus ABR machine has limitation in analyzing hearing level >70dB.

In 2005, Harold et al. proposed that because of lack of sensitivity, ECoG should not play a decisive role in determining the presence or absence of MD [4]. Brendan suggesting the useful role of ECoG in determining a diagnosis of EH with the sensitivity at 1 kHz tone burst test ranges from 50% to 85% [5]. The SP/AP ratio is less sensitive, it has wide sensitivity ranging from 25% to 50%. Meniere's disease (MD) is a very rare and probably underdiagnosed in view of its complex symptoms. Clinical MD is always associated with EH. To fulfill the criterias of definite MD is difficult thus there is limitation in recruiting patients. The nature of disease is episodic and intermittent, making the clinical assessment and audiology test more complicated. Endolymphatic hydrops (EH) was observed in patients with hearing loss, albeit not necessarily fluctuating or in the low frequencies hearing loss. When patients do not exhibiting the classical symptoms of MD this condition is termed "asymptomatic hydrops".

Globally, the incidence and prevalence of MD are not widely reported. Reported prevalence rates of MD have varied widely, with estimates as low as 3.5 per 100,000 and as high as 513 per 100,000 and may also be changing over time [6]. It was stated the prevalence of MD in United States was less than 0.2%. Whereas in Japan, they found a prevalence of EH range from 21.4 to 36.6/100,000 (0.0214%-0.0366%) in two districts [7]. According to Kotimaki et al., the prevalence of MD in Northern European countries approximately 430 cases per million are reported in Finland [8].

A study on prevalence of vestibular problems was carried out by an audiology center of University Kebangsaan Malaysia Medical Centre (UKMMC) in 2011. They found out vestibular problems due to non-otological factor (67.37%) are higher than peripheral causes. There are include vascular (20.3%), neurological (43.8%), metabolical (10.9%), central nervous system (CNS) abnormalities (10.9%), miscellaneous (10.9%) and auto-immune disease (3.1%). Among the peripheral causes of vestibular disorder is less common than central causes; they are due to otological factor (32.63%), BPPV (64.5%), MD (12.9%) and vestibular neuritis (3.23%) [9]. Any of these conditions will cause EH. The methodological differences, the complex criterias for the diagnosis of MD and difficult conditions in distinguishing MD contributed to wide range of results in ITLD and ECoG.

Chapter 2

OBJECTIVES OF THE STUDY

2.1 General objective

1. To establish intertone latency difference (ITLD) as a clinical diagnostic tool for endolymphatic hydrops (EH)

2.2 Specific objectives

1. To determine the mean of intertone latency difference (ITLD) results in patients with endolymphatic hydrops (EH)

2. To determine the correlation between intertone latency difference (ITLD) and electrocochleograph (ECoG) in patient with endolymphatic hydrops (EH)

Chapter 3

MANUSCRIPT

3.1 TITLE PAGE

Research title:

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Conclusion: Since there was no correlation between ITLD and ECoG, ITLD has a role in helping to identify EH however it might not be useful as a diagnostic tool.

Keywords: Meniere's disease, endolymphatic hydrops, auditory brainstem response, intertone latency difference, electrocochleography

3.3 INTRODUCTION

Endolymphatic hydrops (EH) is a disorder of the vestibular system of the inner ear consists of abnormal fluctuations in the endolymph fluid which fills the membranous labyrinth. The overproduction or malabsorption of endolymph causes an abnormal increased volume of endolymph in cochlear, resulting in gross enlargement or distension of membranous labyrinth. The primary idiopathic EH is known as Meniere's disease (MD).

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3.4 METHODOLOGY

Research design and setting

This was a cross-sectional study by selecting patient with endolymphatic hydrops (EH) based on clinical symptoms and results of pure tone audiometry (PTA). The participants were recruited from Otorhinolaryngology (ORL) clinic, Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan. The sample size estimation was based on correlation using citation Najib MY (2015), Sample Size Calculator for Correlation Analysis v3.0, Unit of Biostatistics & Research Methodology, School of Medical Sciences, Universiti Sains Malaysia Kubang Kerian Kelantan. The study protocol was approved by the ethical committee HUSM. A total of 14 patients (4 with definite Meniere's disease (MD) and 10 with probable MD) participated in this study. It was conducted for 10 months duration from April 2016 until February 2017. Auditory brainstem response (ABR) was performed followed by electrocochleograhy (ECoG).

Research instruments and methods

The device used for ABR was AEP Biologic System (Navigator.PRO) (Fig. 3) to determine the latency for each frequency tested (0.5, 1.0, 2.0 and 4.0 kHz). The ABR waveforms (1-V) normally occur within a 10-millisecond (ms) time period after an auditory stimulus presented. Only wave V latencies were taken because of its most prominent and most robust wave pattern. Wave V was easier to be recognized in ABR recording. Brief tone stimulation is the most effective stimulus for ABR because it is frequency specific [23] and was used in this study.

The ABR test was carried out in ORL clinic, HUSM (in a sound proof room). The patient underwent otoscopic ear examination and PTA before ABR. The electrodes were fixed to the skin: a) at the vertex (positive), b) at both mastoid regions (negative), c) at the forehead (ground)

(Fig 4a & b). The impedance of electrode was checked and maintained ≤5 ohms during testing. First, a tone burst stimuli was delivered to the tested ear at 500 Hz frequency. The intensity/ amplitude of sound stimuli were at the hearing threshold. Subsequently, the test was repeated at 10-20dBSL (sensation level) above the hearing threshold until the best hearing level. The hearing level more than 70 dB not tested for ITLD due to machine limitation. Subsequently, similar test was repeated at 4 kHz frequency. Similar procedure was done at contralateral ear. The elicited waveform response was measured by surface electrodes. A tone burst evoked potential with reliable specific threshold and frequency was generated, the signal transmitted to the cochlear nerve and brainstem pathway. The amplitude (micro voltage) of the signal was averaged and charted against the time (millisecond), much like an electroencephalography (EEG). Latencies of wave V for the frequencies 0.5 and 4.0 kHz were determined.

The ABR recording parameters: Transducer: inserted earphone, type of stimulus: tone burst, stimulus rate: 13.3/s, polarity:rarefaction, ramping: blackman , duration: 2-0-2, time window: 10.66 ms, filter bandwidth:100-1500 Hz, insert delay: 0.8 ms, intensity step: 5, number of sweeps: 2000, gain: 100000 (Fig. 9). The latencies of wave V were recorded and interpreted (Fig. 11).

The Sanibel tympanic electrode was used for ECoG (Fig. 5, 6). Electrodes were placed to the areas: a) At the forehead (ground), b) Tympanic electrode for ECoG (introduced into tested ear canal), and c) At contralateral mastoid region (reference). The tympanic electrode for ECoG with electro gel was placed gently onto tympanic membrane without doing a myringotomy. With the guidance of endoscope, the tip of electrode was ideally placed at posterior-inferior quadrant of tympanic membrane. The inserted earphone was placed properly over tested ear canals (each time tested on one ear). Impedance was checked below 40 ohms . A click stimulus at amplitude

90dB was delivered through earphone. The base, SP and AP were identified and recorded. It is an effective stimulus for both ABR and ECoG. Click has a greater accuracy to detect the SP on ECoG [10] and we did not require frequency specificity in ECoG.

Recording parameters for ECoG were documented: transducer: inserted earphone, type of stimulus: click, stimulus rate: 7.1/s, polarity: alternating, click duration: 100 usec, Epoch: 10.66 ms, blocking: 1.00 ms, filter bandwidth: 10-1000 Hz, insert delay: 0.8 ms, intensity step: 5, number of sweeps: 1000, gain: 30000 (Fig. 10). Figure 11 showed wave V latencies in ABR and figure 12a &b showed the SP and AP detected from ECoG.

Statistical analysis

The collected data of ABR wave V intertone latencies and SP/AP ratios were entered and analyzed by using SPSS version 22.0. For this descriptive analysis, a non-parametric analysis was applied. Based on small sample size, Mann-Whitney test was used to determine the mean of ITLD. Spearman rho correlation was applied to determine the correlation between ITLD and ECoG. The continuous variables was described either in mean or/and standard deviation (Fig. 2-6). Statistical difference was considered significant at the $p < 0.05$ level.

3.5 RESULTS

This study involved a total of fourteen patients with EH. The subjects range from 18 to 67 years old with the median age of 50 years (Table 1). In view of small number of sample, data distribution of each type of variables was not considered. It was directly reported in the median and interquartile range. Thirteen (92.9%) subjects were males and 1 (7.1%) were female (Fig. 2). The median age and sex distribution were shown in Fig. 1.

We had a total of 4 definite MD and 10 probable MD patients according to clinical assessment. Eleven subjects presented with unilateral hearing loss whereas 3 with bilateral hearing loss. Out of total 14 subjects, 1 had mild HL, 2 were diagnosed mild to moderate HL, 9 patients with moderate HL meanwhile 2 had moderate to severe HL.

All patients underwent bilateral hearing assessments. We performed ABR to measure the ITLD in our subjects. The wave V latency of 500 Hz and 4 kHz were measured and documented. The transit time faster than 10 ms was considered significant.

For right ear assessment from our patients, we found 2 mild to moderate HL, 3 patients had moderate HL and 1 with moderate to severe HL. In left ear test, there was 1 mild HL, 9 patients had moderate HL and 1 with moderate to severe HL. For data which showing skewed distribution, result will be reported in median (interquartile range); categorical variables will be described in frequency and percentage.

The mean of ITLD results in patients with EH between both right and left ears (Table 2, 3) and different severity of HL (Table 4, 5) was compared in between 500 Hz and 4 KHz. The results were compared by Mann-Whitney Test. The two median different intertone latency for

right and left ears were not significantly different ($p>0.05$) between different severity of HL (Table 6).

After completing ITLD test, all subjects went through ECoG test. A SP/AP ratio of ≥ 0.42 in ECoG indicates presence of EH. The SP and AP of both ears (diseased and non-diseased ears) were measured and documented (Table 7). The correlation between ITLD and ECoG in patient with EH was determined by using Spearman's Correlation Test (n=14) (Table 8). There is no significant correlation between the SP/AP ratio and ITLD ($p>0.05$). The observed correlation coefficient, spearman's rho is not interpretable.

3.6 DISCUSSION

When comparing the transit time of wave V between 500 Hz and 4 KHz, we found there was no difference in ITLD in all 14 subjects. The tables displayed the mean of ITLD were all normal. The velocity of this travelling wave is very fast at the base of cochlear, nearly instantaneous for frequency above 4 kHz (in the range of tens to hundreds of microseconds). Later at the apex of cochlear, the velocity of travelling wave noted slow down dramatically [11]. Gerd et al. published a normative data of travelling wave velocity (TWV) test for bilateral ears in diagnosing MD in 2007 [12]. They used the click stimuli to calculate the latency shift at wave III and wave V; in addition a high pass filtered noise also used at frequency 1650 Hz and 6600 Hz. Whereas tone burst stimuli were used in our ITLD test and we only focused on wave V Their ECoG used both click and tone burst stimuli. They also compared the results with transtympanic ECoH Based on the work of 9 patients were included (all definite, probable and possible MD), the TWV were normal and not associated with symptoms of MD. Likewise their ECoG results were corresponded to TWV tests, both were not significant.

The mean travelling wave velocity (TWV) in normal population found in a variable range. Thornton and Farrell proposed in 1991, a normal TWV ranged from 3.1-24.8 ms [13]. Donaldson and Ruth reported the normal population had value between 1.2-11.11 ms but in cases of EH there were no significant difference value [14]. As further study progress until 1994, Kim et al. discovered a higher TWV in patients of MD (23.2 ms at 8 kHz) [15]. However this study had limited subjects which only 7 in total and there was only limited data proposed. Again the value was revised in 2007, Gerd et al. reported the mean TWV in cochlear hydrops was 22.19 ms [12]. In view of different studies were done with different specific method, this made us difficult

to identify a standard cut off point for mean of TWV. The Intertone latency difference was closely related to changes in TWV. The faster cochlear travelling wave causes a shorter ITLD.

From literature reviews, those authors had similar objective which aimed to prove the difference range of TWV and ITLD in EH. Theoretically, a decreased stiffness in cochlear basilar membrane and an increased in solidity of medium for sound transmission occurred in EH. These factors contributed to an estimated shorter latency difference and a higher TWV. In our study, when tested wave V latency at between 500 Hz and 4 kHz, there was no reduced transit time of sound wave from high frequency to low frequency (< 10 ms). In addition, the wave V morphology was found normal. This implicates a normal TWV in EH as there was no shorter latency difference at wave V. Thus the mean of ITLD of ABR was not significant in patients with EH (Tables 2-5).

Don et al. [16] also used an observed ABR to diagnose the presence of cochlear hydrops. His study was performed in 2005 using click stimulus and 500 Hz high passed noise for masking while tested latency shift of wave V in normal hearing and MD subjects. They reported that in masking condition, MD showed wave V that was not broad and the latency was very short. Meanwhile for normal hearing subject, the 500 Hz high-pass response was broader and the wave V latency was delayed/ longer. While testing in unmask condition, MD showed a higher high-pass response. They recorded in MD, the latency difference between the unmasked click alone response and the 500 Hz high-pass masked response was much shorter due to an greater "undermasking" wave V component. This "undermasked component" had a mean shift of 1024 ms in normal hearing subjects and -0.004 ms in the MD subjects. By applying a latency difference of 0.3 ms, they concluded CHAMP test (Cochlear Hydrops Analysis Masking Procedure) had 100% sensitivity and specificity in diagnosing MD.