

Mild Cognitive Impairment does not Affect Pattern Electroretinogram in the Elderly - A pilot Study (Kecelakaan Kognitif Ringan tidak Memberi Kesan pada Pola Elektroretinogram dalam Kalangan Warga Tua - Kajian Awal)

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ABSTRACT

The purpose of this study was to examine the effects of mild cognitive impairment on pattern electroretinogram (pERG) among urban elderly Malays. A total of 36 subjects aged 60 years and above comprising of 18 MCI subjects and 18 normal controls were recruited for this study. The inclusion criteria for both the MCI and normal subjects included best corrected distance visual acuity $\geq 6/9$ (Snellen) with refractive error less than ± 4.00 DS and/or ± 2.00 DC (astigmatism), near visual acuity $\geq N8$, absence or no previous history of any significant media opacities, retinal disorders and ocular pathologies. pERG was recorded with the RetiPort/Scan21 system in accordance with the International Society for the Clinical Electrophysiology of Vision standards. The target presented to subjects through a 19" CRT monitor was a black and white reversing checkerboard with luminance equal to 80 cd/m^2 , contrast 97% and stimulus frequency 2.00 Hz (4 rev/s). Amplitudes and implicit times of P50 and N95 waves generated by the system were noted and compared between the two groups. The results showed no significant difference in the amplitude and implicit times between the right and left eyes so only the right eye was used for comparison between the MCI and control groups. The mean amplitude and implicit times of the right eye of the MCI and control groups were $1.86 \pm 0.65 \mu\text{V}$, $56.27 \pm 6.20 \text{ ms}$ and $1.54 \pm 0.74 \mu\text{V}$, $56.15 \pm 4.98 \text{ ms}$, respectively. T-test showed no significant differences in pERG amplitudes and implicit times between MCI and the control groups. In conclusion, our results may imply that the inner retina is intact in early MCI elderly subjects.

Keywords: Elderly; mild cognitive impairment; pattern ERG

ABSTRAK

Penyelidikan ini bertujuan untuk mengkaji kesan kecelakaan kognitif ringan (MCI) pada elektroretinogram (pERG) dalam kalangan warga tua Melayu di bandar. Seramai 36 orang subjek berumur 60 tahun ke atas terdiri daripada 18 orang subjek MCI dan 18 orang subjek normal sebagai kumpulan kawalan telah diambil ke dalam kajian ini. Kriteria kemasukan bagi kedua-dua kumpulan MCI dan kawalan termasuk ketajaman penglihatan terbaik dengan pembetulan $\geq 6/9$ (Snellen) dengan ralat refraksi kurang daripada ± 4.00 DS dan/atau ± 2.00 DC (astigmatisme), ketajaman penglihatan dekat $\geq N8$, tidak mempunyai sejarah kelegapan media, gangguan retina dan patologi okular. pERG direkodkan mengikut piawaian Persatuan Antarabangsa untuk Elektrofisiologi Klinikal Penglihatan. Sasaran petak segiempat berbalik hitam dan putih diberikan kepada subjek melalui monitor CRT 19" dengan kegerlapan bersamaan 80 cd/m^2 , kontras 97% dan frekuensi stimulus bersamaan 2Hz (4 rev/s). Amplitud dan masa tersirat P50 dan gelombang N95 yang dijana oleh sistem tersebut dibandingkan antara kedua-dua kumpulan. Keputusan kajian menunjukkan tiada perbezaan yang ketara dalam amplitud dan masa tersirat antara mata kanan dan kiri, oleh itu hanya mata kanan digunakan untuk perbandingan seterusnya antara kumpulan MCI dan kawalan. Min amplitud dan masa tersirat pada mata kanan MCI dan kawalan adalah $1.86 \pm 0.65 \mu\text{V}$, $56.27 \pm 6.20 \text{ ms}$ dan $1.54 \pm 0.74 \mu\text{V}$, $56.15 \pm 4.98 \text{ ms}$. Ujian t menunjukkan tiada perbezaan bererti dalam pERG amplitud dan masa tersirat antara kumpulan MCI dan kawalan. Kesimpulannya, keputusan kajian ini mungkin membayangkan bahawa bahagian dalam retina masih dalam keadaan baik pada subjek warga tua MCI peringkat awal.

Kata kunci: Kecelakaan kognitif ringan; paten ERG; warga tua

INTRODUCTION

Mild cognitive impairment (MCI) is defined as a transitional phase between normal aging and dementia, characterized by cognitive decline with normal activity in daily living functioning (Gauthier et al. 2006). However, patients with MCI eventually experience progressive deterioration in their abilities to perform activities of daily living when cognition, behavior and visual disturbances supervene. It has been

reported that older adults with MCI have an increased risk of developing dementia particularly Alzheimer's disease (AD) and an increased mortality rate compared with adults with normal cognitive function (Bennett et al. 2002). According to Petersen criteria (Petersen et al. 1999) the progression rate to AD in community-dwelling older adults with MCI is 12% per year, compared with a rate of 1-2% in adults without MCI. However, the possibility exists that

individuals may remain in their stage of MCI or reverts to normal cognitive function (Amieva et al. 2004; Fisk et al. 2003).

Over the past decades, interest has been growing in determining the predictors of AD. Accordingly, researchers efforts have been devoted to early pre-dementia stage of AD. There is now wide acceptance of the term MCI, when subjects typically present with memory complaints and show deficits on neuropsychological tests, but do not fulfill the clinical criteria for dementia.

Mendez et al. (1990) examined 30 community-based AD patients, 13 (43%) of whom had complex visual complaints. The AD patients were impaired in the visual evaluation of common objects, famous faces, spatial locations and complex figures. In an attempt to explain the visual symptoms of patients with AD, pathological and neuroimaging studies have been carried on the retina, optic nerve and visual cortex. Some studies suggested that patients with early AD showed degeneration of optic nerve, specifically affecting the ganglion cells and its axons in the retina (Berisha et al. 2007; Danesh-Meyer et al. 2006; Syed et al. 2005).

Electrophysiological studies such as pattern ERG has the potential to detect abnormalities of the inner retina, including that of the ganglion cells in the inner retina, manifested by its bioelectrical activity. Abnormalities in pERG test have been reported in patients with AD (Krasodomska et al. 2010; Parisi et al. 2001). Parisi et al. (2001) showed a significant increase in latencies of N35, P50 and N95 waves and a decrease in their amplitudes. Additionally, the increase in latency of P50 wave and a decrease in amplitudes in the P50 and N95 waves correlated significantly with a decrease in thickness of the nerve fibre layer, which they measured using Optical Coherence Tomography (OCT) (Ikram et al. 2012; Lu et al. 2010).

Studies that address the effect of MCI on pERG are lacking. pERG can be a potential tool to detect early changes in the inner retina. Integrity of the retinal ganglion cells could be linked to neural cell body loss (Parquet et al. 2007). Early identification of MCI may alert healthcare providers on the treatment needed to arrest or delay the progression from MCI to dementia. Therefore, this study aimed to evaluate the integrity of retinal ganglion cells in MCI patients by using pERG.

METHODS

SUBJECTS

This is an analytical and observational study based on convenient sampling. MCI subjects identified from the Kuala Lumpur Ageing Study (KLAS) were invited to participate in this study. Subjects were diagnosed as having MCI by certified clinical psychologist if they met the following conditions: memory complaints; preserved global cognitive functions; intact activities of daily living (ADL) and instrumental activities of daily living

(iADL); not demented; not depressed; and abnormal cognitive impairment for age (Lee et al. 2012). For the MCI subjects, a full optometric examination was carried out and those who met the inclusion criteria were selected for electrophysiological assessment. Control subjects were invited among patients that came to the clinic for eye examination. The control subjects first underwent cognitive status evaluation using MMSE and those who met the minimum score of 27 in the Malay version MMSE were accepted as controls. The Malay version of MMSE was already validated among the local elderly population (Zarina et al. 2007). Similar electrophysiological assessment was carried out among the control subjects. All tests were done at the Clinic and Electrophysiological Lab, Optometry and Vision Sciences Program, Faculty of Health Sciences, Universiti Kebangsaan Malaysia.

The inclusion criteria for MCI patients and their age-matched controls were: best corrected distance visual acuity $\geq 6/9$ (Snellen chart) with refractive error less than ± 4.00 DS and/or ± 2.00 DC (astigmatism); near visual acuity $\geq N8$; absence or no previous history of any significant media opacities, retinal disorders and ocular pathologies. Informed consent was obtained from all subjects enrolled in the study. This experimental protocol was approved by the Research and Ethics Committee of the Medical Research UKM (NN-066-2012) and met the terms set by the Declaration of Helsinki.

SUBJECT PREPARATION AND PERG TEST PROCEDURE

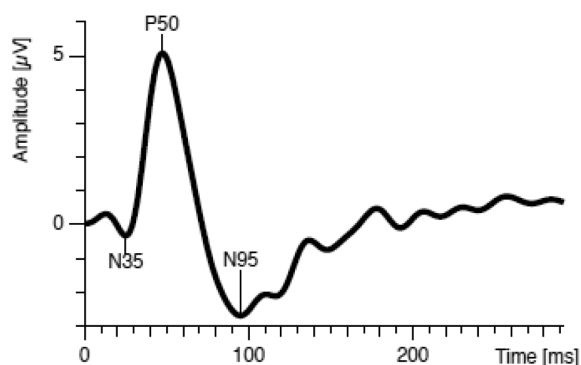
The skin in contact with the reference and ground electrode was first cleaned with Gel-Nu prep and conductive paste-Ten20 applied to ensure good electrical contact. Dawson, Trick-Litzkow (DTL) thread electrodes was used as the active electrode and draped in the inferior conjunctival cul-de-sac from the internal to the external canthi. Gold disc electrode was placed at the ipsilateral outer canthus the reference and at the forehead as the ground. Electrode impedance was kept below 5 k Ω in all cases. Excessive blinking during recording was discouraged and short pauses allowed in between recordings.

pERG was recorded without pupil dilation. Subjects wore the appropriate spectacle correction for the one meter eye-screen distance for recordings. Binocular recording was chosen because of ISCEV recommendation and it is generally more stable, has less recording time and allowed fixation of the better eye in cases of asymmetrical visual acuity (Bach et al. 2013).

pERG was recorded with the RetiPort/Scan21 system (Roland Consult, Brandenburg, Germany), in accordance with standard guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV). The instrument was calibrated every three months according to standard set by the manufacturer.

The target presented to subjects through a 19" CRT monitor was a black and white reversing checkerboard with luminance equal to 80 cd/m², contrast 97% and stimulus frequency 2.00 Hz (4 rev/s). A red cross at the centre of the

screen was used as the fixation target. If it cannot be seen a larger cross was used. Two measurements were recorded and the consecutive waveforms of P50 and N95 (Figure 1) were averaged and analyzed.



Source: ISCEV (2012)

FIGURE 1. A typical standard transient pERG. Amplitude and latencies of P50 and N95 were usually analyzed as they were most stable and prominent components

DATA ANALYSIS

Shapiro-Wilks test showed the data was normally distributed for all parameters ($p > 0.05$) therefore 2-tailed t-test was used to compare results of the MCI and control subjects. Paired t-test was used to compare the mean values for the right and left eyes for all parameters measured: P50, N95, Implicit times for P50, N95 and the results showed no significant differences between them ($p = 0.24 - p = 0.65$), therefore only the right eye was used for subsequent analysis between the MCI and control groups.

RESULTS

There were 18 participants (13 females and 5 males) in the MCI and another 18 participants (2 females and 16 males) in the control group. The mean age for the MCI and control groups was 66.3 ± 3.4 and 64.9 ± 3.9 years, respectively. Our results showed no statistically significant

differences in amplitude and implicit times of the P50 and N95 waveform between the MCI and control group. The results are summarized in Table 1.

DISCUSSION

This study used the pattern electroretinogram (pERG) to examine retinal ganglion cell activities in MCI patients and the results were compared with a control group of age-matched healthy cognitive subjects. There was no statistically significant difference in amplitudes and implicit times of P50 and N95 waves in pERG tests measured in MCI patients compared with controls. External factors such as age, ocular media opacities, refractive error and visual acuity and retinal disorders were controlled in this study prior to pERG recordings. However, the findings of this study might be affected by other factors such as gender, pupil size and different stages of MCI.

In this study, all the MCI and control subjects were age-matched, but not gender matched. There were more females and fewer males in MCI group compared to the control group. Several studies have reported a greater pERG response on women than men (Birch & Anderson 1992; Trick et al. 1992). This was believed to be linked to axial length of the eyeball where men were more likely to have a greater axial length (Chen et al. 1992; Westall et al. 2001). It was possible that the pERG findings were influenced by the unbalanced representation of gender in this study.

ISCEV standard recommends testing of pERG without pupil dilation in order to preserve accommodation and retain retinal image quality (Bach et al. 2013). Therefore the pupil size of all subjects in this study was not taken into consideration. However since all subjects were over 60 years old most probably they have senile miosis. It is known that senile miosis will reduce spherical and chromatic aberration, increase diffraction effects and limit retinal illuminance (Campbell & Green 1965) which may influence the findings of pERG tested, however it will equally affect both the pERG values in the MCI and control groups.

During the time of this study, the MCI subjects enrolled would have been diagnosed for about two

TABLE 1. Amplitude and implicit times of MCI and control

Parameter	Eyes	MCI (N = 18)		Control (N = 18)		2 tailed t-test between MCI and control
		(mean±SD)	95% confidence interval	(mean±SD)	95% confidence interval	
P50 amplitude (µV)	RE	1.86±0.65	1.54-2.18	1.54±0.74	1.17-1.90	t(34) = 1.391, p = 0.173
P50 implicit time (ms)	RE	56.27±6.20	53.19-59.35	56.15±4.98	53.67-58.62	t(34) = 0.067, p = 0.947
N95 amplitude (µV)	RE	2.61±1.16	2.03-3.18	2.60±1.25	1.98-3.22	t(34) = 0.03, p = 0.977
N95 implicit time (ms)	RE	94.66±5.76	91.79-97.52	97.18±6.35	94.02-100.33	t(34) = -1.247, p = 0.221

Significant if $p < 0.05$

years. They did not complain of visual disturbance prior to pERG recordings. There was also a possibility of progression or regression at different degree of their cognitive status. Even within the diagnosis of MCI, it was now possible to delineate and operationally define degrees of severity, with the more severe form representing a group of people who later develop AD (Morris et al. 2001). In a representative survey, Ritchie et al. (2001) showed that the rates of conversion for people satisfying criteria for ageing-associated cognitive decline were three times those for MCI. However this processes is much more complex than previously thought and it was unknown whether there was a linear progression from one stage to another. pERG can certainly be part of the tools to find early changes in the inner retina and visual pathway that connect to the brain.

Studies on early AD have found significant differences in pERG values compared to control healthy elderly. Although there were some similarities between MCI and AD and common etiologies were shared the degrees of morphological and functional changes primarily in the retinal ganglion cells may differ, hence the difference results (Ascaso et al. 2014, Parquet et al. 2007). It may also imply that there was no abnormal pERG responses found in MCI patients in the current study.

Although abnormalities in pERG tests have been reported in patients with early AD (Krasodomska et al. 2010), normal pERG tests results were also observed (Kergoat et al. 2002). Kergoat et al. (2002) showed that some subjects who had dementia of the Alzheimer type (DAT) had normal pERG results compared to controls, indicating that the retina may be spared of the disease process. An interesting finding by Krasodomska et al. (2010) is that Ocular Coherence Tomography (OCT) results were normal but pERG results were abnormal in early AD as compared to controls. This may imply that nerve fibre layer changes detected by pERG precede the structural changes seen at the ganglion cell layers measured by OCT. As such, pERG can be an important tool to be used in early AD and MCI patients in clinical situations.

Our data seems to add on the conflicting reports available on the effect of pERG on mild cognitive impairment. Additional study is already underway to address some of the issues related to sub-type, severity of MCI and confounding factors like gender and pupil sizes. Further investigations may expand to include neuroimaging technique such as Optical Coherence Tomography (OCT) which has good potential in monitoring MCI patients.

CONCLUSION

The pilot study has provided preliminary data that showed the amplitude and implicit times of P50 and N95 waves of the pattern electroretinogram (pERG) responses in Mild Cognitive Impairment (MCI) was not significantly different

from the age-matched controls. This may also be due to gender bias, different subtype and severity of MCI subjects. An additional study is underway to reconfirm the findings.

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