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Original Article

Effect of Hormone Repalcement Therapy on Visual Evoked Potentials in Post-Menopausal Females

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ABSTRACT

Introduction: A normal Visual Evoked Potential (VEP) consists of a series of waveform of opposite polarity. VEP is used a sensitive tool to detect lesions in the visual pathway. Sex hormones are known to exert regulatory influences on the central nervous system and can influence the electrical activities of the brain including evoked responses.

Aims & Objectives: The present study was designed to see the actual effect of Estrogen and Progesterone hormones on VEP in women.

Materials & Methods: Forty Post-Menopausal women were divided in two group; Twenty three females received estrogen only and 17 Females received progesterone only Hormonal replacement therapy, respectively. VEP was measured at baseline and after a spell of Hormonal replacement therapy. Latencies and amplitudes of the first positive wave P100 were compared with the baseline values in the two groups of HRT.

Results: The P100 latencies were significantly (P value=0.0047) decreased after Estrogen supplementation but P100 amplitudes though decreased after therapy but the decrease was not significant (P value=0.20). The P100 latencies were significantly (P value=0.002) increased with Progesterone supplementation but P100 amplitudes though increased after therapy but the increase was not significant (P value=0.6).

Conclusion: The alterations in the latencies and the amplitudes of P100 waves of VEP are thought to result from the different effect of estrogen and progesterone on cortical excitability. This study confirms the fluctuations of VEP with the different phases of menstrual and post-menopausal female life in accordance with different sex hormonal milieu of a female body. Hence such influences should be kept in mind while interpreting such investigations.

KEYWORDS: Amplitude, Latency, Post-menopausal, Visual Evoked Potential.

INTRODUCTION

The Visual Evoked Potential (VEP) is a gross electrical response, which reflects the processing of visual message from the macular area of retina through the visual pathway to the primary visual area of occipital cortex. It is recorded by placing electrodes on the scalp. It is an indirect index of macular function and the integrity of the visual pathway right up to the calcarine fissure of the occipital cortex. As the size of the cortical response to visual stimulation is small in comparison to the background brain activity, response averaging is necessary to obtain measurable VEP records. This is accomplished by presenting visual stimuli repetitively and summing the activity that is synchronized with stimulus onset.

VEPs may be recorded by using either flash stimuli or pattern reversal stimuli (checks or stripes). The pattern reversal response is more sensitive to relatively small changes in visual acuity level as compared to the flash response. The pattern reversal response is also more sensitive to the dysfunctions of the optic nerve and

demyelinating diseases of the optic pathways than the flash response. Hence, the pattern reversal visual evoked potentials are generally more useful than the flash evoked potentials.[1]

A normal VEP consists of a series of waveform of opposite polarity. The negative waves are denoted as N and the positive ones as P. The time taken by any particular wave to appear after the delivery of stimulus is known as latency. Hence N70 means it is a negative waveform which appears 70 milliseconds after presentation of stimuli. The commonly studied waveforms are N70, P100 and N135.[2]

There are many physiological factors which may affect the VEP waveforms, for example, age, gender, pupillary size, eye dominance and eye movement. Measuring technique also has influence on the characteristics of these waveforms.[3,4] It is also used as a sensitive tool to detect lesions in the visual pathway.[5,6]

The reproductive system of female, unlike that of male, shows periodic and pulsatile release of gonadotrophic hormones FSH and LH. This is responsible for the periodic preparations for fertilization and pregnancy. The sex hormones are not only responsible for the appearance and maintenance of secondary sexual characteristics but also play a crucial role during embryological development of individual. They are responsible for sexual differentiation of the brain, by characteristically designing of the pattern and organization of the circuits in specific parts of the brain.[7] Even during reproductive years of life these hormones not only restrict themselves to the endocrine control of the body, but their influence extends to many regions and functional aspects of the central nervous system. Sex hormones are known to exert regulatory influences on the central nervous system in many different ways. Cyclic steroid production during the menstrual cycle in females has been implicated in mood changes,[8] level of different neurotranmitters,[9] convulsability,[10,11] and hyperkinetic movement disorders.[12] It is not surprising therefore, sex steroids can influence the electrical activities of the brain including evoked responses.

Soon after arrival of electrophysiological measuring techniques as electroencephalogram (EEG) and nerve conduction studies it was discovered that there were significant differences in these parameters between males and females. Similar gender differences were expected to exist for evoked potentials also.[13-17] Many studies proved that evoked potential are affected by sex steroids and they also differ during different phases of menstrual cycle.[16-22]

AIMS AND OBJECTIVES

Studies conducted with the intention to delineate the effect of different female sex hormones on Evoked potentials were usually done in normally menstruating women. This study design cannot record the effect of one hormone at a time. It is because, during menstrual cycle one hormone predominates in one phase and the other one does in another phase. There is practically no time in the normal cycle which is predominated by one hormone at a time. During follicular phase effect of estrogen predominates and during luteal phase the progesterone level is higher.

Hence, in order to see the actual effect of these hormones in women, this study was designed. In our present study, a group of 40 post-menopausal females was subjected to hormone replacement therapy (HRT) and its effect on VEP was measured.

MATERIALS &METHODS

The study was undertaken in King George Medical University, Lucknow, UP, India. A group of 40 post-menopausal ladies was selected. A baseline recording of Visual Evoked Potential was taken. The study population was divided into two groups; one with 23 females was given replacement of estrogen only and the other group with remaining 17 ladies was given progesterone only. The Visual Evoked Potentials were again recorded after a spell of HRT and compared with the baseline values. Ethical permission was sought from the ethical committee of the institute. The subjects who met the inclusion criteria and gave informed consent to participate in the study were enrolled.

The inclusion criteria were:

1. A history of menopause of more than 4 years.
2. Absence of any significant physical and/or mental illness which can affect the study for example retinopathy, demyelinating disorders, cataract, glaucoma, and optic atrophy.
3. Age between 45 to 55 years.
4. Normal BMI.
5. Absence of visual defects. Corrected visual acuity 6/6.
6. Absence of any medication with possibility to affect electrophysiological measurements for example antidepressants, opoids, sedatives and antipsychotics.
7. Absence of any personal or family history of seizures.
8. All subjects underwent a clinical examination and a brief psychological interview and no abnormalities were present.
9. Absence of any drug abuse.

Just before recording of the evoked potential the subject was given a brief health checkup, with special attention to body temperature and pulse rate (to rule out febrile condition). To avoid normal circadian variation in the parameters, all the recordings were done in the afternoon. Table-1 shows the clinical characteristics of the subjects.

NEUROPACK FOUR model MEM-4104K, manufactured by Nihon Kohden Corporation was used for recording the visual evoked potentials. Two hundred epochs were averaged to ensure a clear potential. For judging the reproducibility of the waveform, they were

twice averaged and superimposed. The recording electrode is placed at occiput using jelly or electrode paste as per 10- 20 international system of electrode placement.[23] The reference electrode is placed 12 cm above the nasion. Linked ear reference is also used as non-cephalic reference. The ground electrode is placed at the vertex. The electrode impedance is kept below 5 Kohm. An amplification ranging between 20,000 and 1,00,000 is used to record pattern reversal visual evoked potentials. The filter settings were kept constant to avoid variations in latencies in the test series. The test was conducted in a dimly illuminated room with non-distracting background and subjected seated in an upright position. The subjects were asked to avoid hair spray or oil and any mydriatic or miotic eye drops 12 hrs before the test.

Table-1. Clinical Characteristics of the Subjects

Number of Subjects (n)	40	
Variables	**Mean**	**SD**
Age	49.90 years	± 8.26
Body Weight	66.35 kgm	± 5.21

Table 2: P100 Latency and Amplitude before and after Estrogen Therapy.

No. Of subjects	Mean P100 latency (ms)		SD		P value
	Before Estrogen	After Estrogen	Before Estrogen	After Estrogen	
	121	116.125	± 9.767	± 10.266	.0047
	Mean P100 amplitude (mV)		SD		
23	Before Estrogen	After Estrogen	Before Estrogen	After Estrogen	P value
	12.206	11.202	± 3.827	± 4.031	0.20

Table 3: P100 Latency and Amplitude before and after Progesterone Therapy.

No. Of subjects	Mean P100 latency (ms)		SD		P value
	Before Progesterone	After Progesterone	Before Progesterone	After Progesterone	
	113.425	116.8	± 8.802	± 6.858	0.002
	Mean P100 amplitude (mV)		SD		
17	Before Progesterone	After Progesterone	Before Progesterone	After Progesterone	P value
	11.202	12.283	± 4.031	± 3.949	0.06

RESULTS

Latencies and amplitudes of the first positive wave P100 were compared with the baseline values in the two groups of HRT as shown in Table-2.

The P100 latencies were significantly (P value=0.0047) decreased after Estrogen supplementation but P100 amplitudes though decreased after therapy but the decrease was not significant (P value=0.20).

The P100 latencies were significantly (P value=0.002) increased with Progesterone supplementation but P100 amplitudes though increased after therapy but the increase was not significant (P value=0.6) as shown in Table-3.

DISCUSSION

This study was undertaken to answer certain queries, regarding relationship of electrophysiological parameters with the two female hormones. Not much is known about the behavior of Visual Evoked Potentials during the sexual cycle of females and how the latencies & amplitude of different VEP waveforms vary with the hormonal milieu of the female body.

In our study it was found that estrogen is responsible for decrease in latency and amplitude of P100 wave. On the other hand it was seen that progesterone is causing increase in both latency and amplitude of P100 wave. Although the changes produced in amplitude were not significant statistically.

Similar findings were obtained by Knaeda et al and Yilmaz et al but their studies were performed in different phases of normal menstrual cycles which are predominated by either of these hormones at a time.[20,21]

Many studies comparing gender differences have documented shorter latencies and higher amplitudes in females which may be due to the effect of estrogen and progesterone respectively.[24-29] Studies like have found no gender differences in P100 latencies and amplitudes hence ruling out effect of hormones on these parameters.[18,19,30-32] Certain studies have implicated anatomical peculiarities along with endocrine factors behind gender differences.[33]

These alterations in the latencies and the amplitudes are thought to result from the different effect of estrogen and progesterone on cortical excitability. Hormonal changes that occur during the menstrual cycle of women also influence the visual function of females. Estrogen is reported to cause a decrease in the visual transmission time by increasing the sensitivity of receptors in the optic pathways to dopamine.[21] Progesterone tends to reduce neuronal excitability, raising the seizure threshold and exerting effects on behavior like those of anti-anxiety drugs. Progesterone is thought to produce these effects by binding to a site on GABA-A receptor. This increases the receptor's affinity for GABA, which is responsible for opening of Cl^- channels on the neuronal membrane. Benzodiazepine and similar agents bind to a separate site of GABA-A receptors and affects its affinity for GABA in a similar way.

In contrast estrogen has opposite effects on the seizure threshold and other measures of neuronal excitabilty.[34,35] Although the exact mechanism of action of estrogen on the neuronal excitability and conductivity is not clearly understood. It is thought to be involved in allosteric interaction with the N-methyl-D-aspartate (NMDA) receptor for glutamate, and excitatory neurotransmitter which mediates the membrane permeability for Na and Ca ions.[36] It has been seen that estrogen down regulates 5-hydroxytryptamine receptors in motor[37] and frontal[38] cortex, which modulates GABAergic transmission.[39] Estradiol has also been shown to exert trophic effect on cultured neocortical neurons.

As estrogen is present in both the phases of menstrual cycle, it is not possible to assess its effect on neuro-electrical parameters in normally menstruating women. However, the relative lack of inhibition in the follicular phase may unmask its effect on neuronal excitability. Hence the best setup to register the individual effect of estrogen and progesterone on VEP waveforms was to see it in postmenopausal women, by supplementing them with either of these hormones, one at a time.

CONCLUSION

Cyclic changes in hormones, body temperature and metabolic rate characterize the female sexual cycle. Post-menopausal state is unique as it is characterized by absence of any female sex hormones. All these parameters and variables have great influence on various electrophysiological measurements including Visual Evoked Potentials. The results of this study reemphasize the basic sex differences in the organization of the brain. It also confirms the fluctuations of these parameters with the different phases of menstrual and post-menopausal female life. Hence such influences should be kept in mind while interpreting such investigations. Our study has successfully clarified the effect of female sex hormones on the waveforms of Visual Evoked Potentials.

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