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AUDITORY EVOKED RESPONSES IN POSTMENOPAUSAL WOMEN ON HORMONE REPLACEMENT THERAPY

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Abstract : The effect of hormone replacement therapy (HRT) was studied in 32 postmenopausal women on their auditory Evoked Potentials i.e. auditory brainstem response (ABR), Middle latency response (MLR) & slow vertex response (SVR). Recordings were done on computerized evoked potential recorder using 10/20 system of electrode placement and standard click stimuli. A significant improvement in neural transmission was observed as was evidenced by decrease in the ABR wave latencies I, III, IV & V and interpeak latency III-V and I-V after 6 months of HRT. A similar significant decrease was observed in MLR wave latencies of Po, Na & Pa. The SVR wave latencies although found to be decreased after HRT, could not reach the level of statistical significance. There was a significant inverse correlation obtained between latencies of wave I in ABR, Po in MLR and serum estradiol. The results indicate the effect of sex hormone in improving transmission in auditory pathway from periphery through brainstem, thalamus upto cortex. However slow vertex responses indicate that auditory association areas are not much affected. This might have bearing on improvement of neuropsychological functions in postmenopausal women on HRT.

Key words : hormone replacement therapy, menopause, auditory evoked responses, auditory brainstem response, middle latency response, slow vertex response

INTRODUCTION

The consistent and dramatic increase in female life expectancy during the past century means that women now live one third of their lives beyond cessation of their reproductive capacity. The notion of maintaining psychological and intellectual functioning in old age has stimulated a great deal of research in neuroscience in recent years. The search for a biochemical or anatomical underpinning for changes in brain functions with increasing age has found a focus in the sex hormones, the concentrations of which decrease profoundly at midlife in women as a result of ovarian atrophy.

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Previously it was thought that hormone replacement therapy (HRT) in menopausal women influences only sexual behavior but now it is known to influence many CNS functions also like thinking, learning and memory (1, 2).

Evoked potential responses (EPR's) which are indicators of functional integrity of sensory and cognitive pathways were influenced by both age and gender (3, 4) but larger age effect occurred for the female subjects. This does not dispute an anatomical explanation for the gender effect seen in old age, but hormonal changes accompanying menopause may also account for some of the gender differences noted in ABR.

We had earlier conducted a study of EPR in normal menopausal females and found significant deviations of EPR latencies from the normal adult females. The hormonal hypothesis was proposed to account for these changes (5). In addition to auditory brainstem response (ABR-obtained within 0-5 ms of application of stimulus), the middle latency response (MLR 8–50 ms) and slow vertex response (SVR > 50 ms) were also studied so as to scan a wide tract of auditory pathway i.e. from auditory nerve to auditory cortex and association areas.

As an extension to our earlier work we now propose to evaluate the effect of hormone replacement therapy in postmenopausal women on neuropsychological functions by way of auditory evoked responses.

METHODS

Thirty-two women between 50 and 70 years of age who had attained natural menopause (without surgical removal of ovaries) for at least one year were selected from Gynecology OPD over a period of eighteen months i.e. between January 2000 and June 2001. Except for post-menopausal symptoms like hot flushes, night sweats, insomnia and mood swings, these patients were free from any medical ailments.

Evoked potential responses were recorded on them before starting a course of hormone replacement therapy. They were subsequently given continuous sequential regimen which consisted of conjugated equine estrogen 0.625 mg daily throughout the month and progesterone 10 mg daily for 12 days a month. After 6 months of HRT a second recording of EPR's was done. A battery of clinical tests, which include serum estradiol, lipid profile, blood sugar, mammography and Pap smear, was performed on subjects before starting HRT.

The recordings were taken on computerized evoked potential recorder (MEB 5200 Nihon Kohden, Japan). The subjects were lying down and relaxed at the time of testing in soundproof air-conditioned room. EPR's were obtained from Ag/AgCl disc electrodes affixed with collodion at 10/20 international placement (6). Positive electrode was kept at Cz position, negative (reference) at ipsilateral ear lobule (A_1) and the ground electrode at the forehead. The contact impedance was constantly monitored with an impedance meter and electrode to skin contact resistance was kept below 5 k ohm. Alternating clicks at the rate of 10/sec were delivered at 90 dB SPL through shielded earphones with-40 dB pure white noise masking of the contralateral ear. For ABR this was then filtered (with band pass

150–3000 Hz) and averaged to 2048 stimuli. Recordings were obtained from each ear separately in duplicate. The absolute peak latency, interpeak latency and amplitude of waves were measured with cursors on the screen. For MLR 256 clicks were given at alternate polarity for 0.1 ms at the rate of 5/sec, at intensity of 90 dB. SVR was measured by giving 64 clicks of alternate polarity for 0.1 ms at the rate of 0.5/sec and at same sound intensity.

Statistical Method: Paired Students 't' test was used to compare the pre and post therapy values of various parameters. Correlations between Auditory evoked responses, duration of menopause and serum estradiol were derived by Bivariate correlation and simple regression analysis.

RESULTS

The ABR (Table I) latencies of waves I, III, IV, V and inter peak latencies I–V and III–V were significantly decreased ($P<0.05$) after 6 months of HRT while the amplitudes of waves I and V were significantly increased as compared to the recordings taken before starting HRT ($P<0.05$).

MLR (Table II) latencies of waves Po, Na and Pa were significantly less ($P<0.05$) after HRT. The latencies of waves No and Nb were also decreased after HRT but the values could not reach the level of significance.

In SVR (Table III) the trend is towards a decrease in latency of all the waves but it could not reach the level of significance.

TABLE I: ABR in menopausal women.

	No. of women (n)	*Latencies (msec)*					*Interpeak latencies (msec)*			*Amplitude (mV)*		
		I	*II*	*III*	*IV*	*V*	*I-III*	*I-V*	*III-V*	*I*	*III*	*V*
Before HRT	32	1.68 ±.13	2.71 ±.14	3.88 ±.22	5.16 ±.46	5.85 ±.28	2.20 ±.27	4.17 ±.29	2.33 ±.38	0.33 ±.02	0.35 ±.02	0.37 ±.03
After HRT	32	1.49 ±.02*	2.56 ±.43	3.59 ±.22*	4.85 ±.32*	5.61 ±.30*	2.10 ±.23	3.86 ±.39*	1.96 ±.29*	0.36 ±.01*	0.36 ±.03	0.41 ±.02*

*P<0.05

TABLE II: MLR latencies (m sec) in menopausal women.

	No. of Women (n)	*No*	*Po*	*Na*	*Pa*	*Nb*
Before HRT	32	9.96±.35	14.09±.52	17.25±.45	24.81±.46	38.09±.99
After HRT	32	9.82±.67	13.15±49*	16.25±.48*	20.41±.75*	37.51±1.05

*P<0.05

TABLE III: SVR latencies (m sec) in menopausal women.

	No. of Women (n)	P_1	N_1	P_2	N_2
Before HRT	32	51.13±3.3	94.36±2.75	183.72±5.14	257.15±4.3
After HRT	32	50.96±2.8	93.54±2.5	182.71±4.51	255.43±3.6

*P<0.05

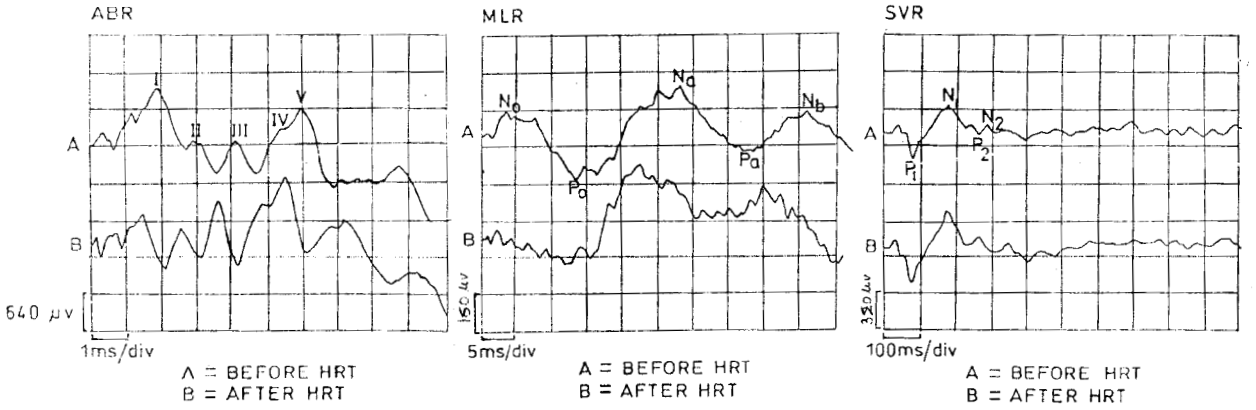

Fig. 1

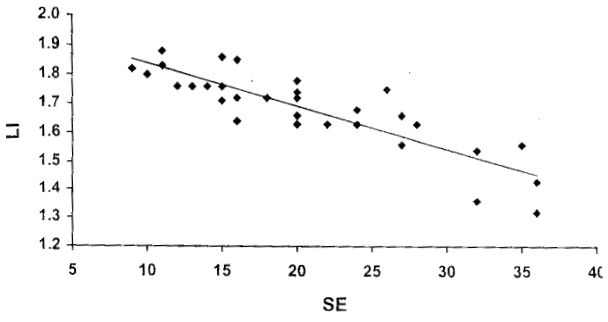

Fig. 2: Correlation of Serum estradiol with latency of Wave I in ABR.

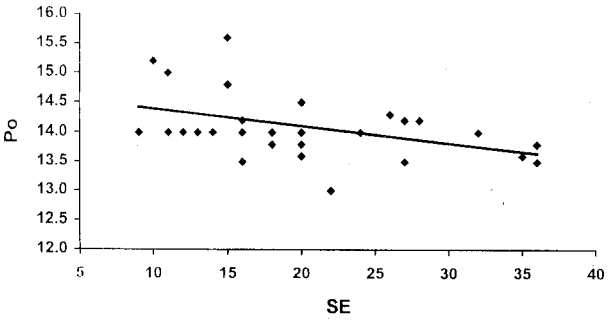

Fig. 3: Correlation of Serum estradiol with 'Po' wave of MLR.

The tracings of ABR, MLR and SVR waves in a subject before and after HRT are shown in Fig. 1.

There was no correlation between the auditory evoked responses and duration of menopause in both the pre and post therapy groups, while the serum estradiol level showed a significant inverse correlation with latency of wave I in ABR (Fig. 2) in the pre therapy group. The other waves of ABR were also inversely correlated with serum estradiol, but could not reach the level of significance. Similarly there was a significant

inverse correlation of serum estradiol with 'Po' wave of MLR (Fig. 3) in the pre therapy group. Even the other waves of MLR were inversely correlated with serum estradiol but they could not reach the level of significance. There was an inverse correlation between serum estradiol and different waves of SVR, but none of them could reach the level of significance.

DISCUSSION

The results of the present study support the notion that sex hormone have a role in improving the neuropsychological functions in postmenopausal women. In ABR the latencies of waves I, III, IV, V & inter peak latencies I–V and III–V decreased significantly while amplitudes of wave I and V increased after 6 months of hormone replacement therapy. These parameters were earlier reported by us to be increased in menopausal females as compared to young adult females pointing towards a delayed neural transmission due to changed hormonal milieu of sex hormones after menopause (5).

Similar studies done in young adults also indicated sex-related changes in auditory evoked potential responses. All the absolute peak latency and inter peak latency values in female subjects were significantly lower than age matched males, while amplitude of waves I and V were higher. It was concluded that with increased production of estrogens and progesterone in females after puberty, the neural transmission and conduction velocity in auditory pathways is much better than in male's (4). Similar changes were observed by other workers (7, 8). It was presumed that hormonal milieu cause sex difference in ABR. There were reports of interactions between estrogen and Acetylcholine for improvement of sensory transmission (9, 10) and the possibility of Acetylcholine as one of the neurotransmitters in auditory pathway (11). Therefore in young adult females, with onset of increased production of estrogen and progesterone the neural transmission and conduction velocity in auditory pathways was much better than in males. This is also an explanation of our results of ABR, which showed a significant improvement in neurotransmission as observed by decreased latencies of waves I, III, IV & V and interpeak latencies I–V and III–V. Since inter peak latencies indirectly reflect conduction time in the auditory pathway, the decrease in their values indicate an improved transmission. The inter peak latency I–III was also decreased after HRT but could not reach the level of significance. This can be due to less influence of sex hormones at lower levels of auditory pathway. Our results are in line with similar studies on ABR in postmenopausal women on HRT (12) or a synthetic steroid tibolone (13).

In middle latency response (MLR) the latencies of waves Po, Na and Pa decreased significantly after HRT in the present study. Pa is the most prominent component among the five defined components of MLR (14). According to a hypothesis proposed by Gee (1988) Pa latency assesses time of peak neural activity. An improvement in Pa latency in the present study gives an indication of improvement in the conduction of central auditory pathway as well. The latencies of most of the waves of MLR were

significantly lower in young adult females as compared to males. But this difference disappeared in elderly subject's (15). This was not due to smaller size of brain in women and hence a shorter neural transmission pathway because the difference disappeared at a later age. This could also not be explained on the basis of marked cerebral involution in elderly women. Since electrophysiological studies demonstrated a predominance of low rhythms (relative delta activity) in elderly men, whereas in elderly women, the relative beta activity prevailed, an index of a more marked aging process in male's (16). Hence the hormonal hypothesis again stands true for MLR's since their latencies are observed to be significantly improved in women on HRT. MLR's, by exploring a wide tract of the auditory pathways and specifically the thalamocortical projections upto the primary auditory area are a more complete and appropriate responses than ABR's alone in such studies.

In the SVR there was no significant difference obtained on HRT in the present study. This can be explained as these components have widespread distribution over the fronto-parietal scalp area (17) and it is difficult to pick them up by a single active electrode. Even if they are located precisely, they do vary with certain factors like sleep and level of alertness (18). Hence MLR's are a more sensitive indicators of conduction in higher auditory pathways.

In the present study the duration of HRT was chosen as 6 months to study the effect of auditory evoked responses. This is in accordance to the convention, as in earlier studies done on HRT a significant effect is observed in either 3 or 6 months of therapy (19, 20). We chose 6 months to see the more stabilized effect.

There was a significant inverse correlation obtained between latency of wave I ABR, Po in MLR and serum estradiol in the pre therapy group. This indicates that as the serum estradiol is decreasing after menopause there is increase in latencies of above mentioned waves further confirming a delay in neural transmission after menopause. This finding could not be compared with previous studies, as the literature is deficient in such correlation. To confirm the above findings, the study can be further extended, by including surgically menopausal women who are only estrogen therapy and measuring the above parameters in them.

The present study, thus reveals that improved auditory conduction in peripheral (ABR) and central (MLR) auditory pathways, facilitates the process of sensory perception, which may form one of the mechanisms of improved neuropsychological functions in menopausal women on HRT.

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