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Original Article

Studying the Inter-Peak Latencies of Auditory Brainstem Response in Menopause Women

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Abstract

Background: Changes in auditory function have been noted in post-menopausal women attributed in part to the lower levels of ovarian hormones. Decreased levels of ovarian hormones may alter auditory neurotransmission time, as evaluated by Auditory Brainstem Responses (ABR). Thus, objective of this study was comparison of mean inter-peak ABR latencies in post-menopausal women compared to non-menopausal women.

Methods: In this cross-sectional study, research sample consisted of 60 women as case group in the age range of 45-55 years, who were post-menopausal and had normal hearing. The control group with similar characteristics were non-menopausal. Two groups were estimated by ABR and then the means of the variables that had a normal distribution were compared with each other by independent t-test.

Results: All differences between two groups were not significant, as follows; Mean I-III inter-peak ABR latencies (p-value=0.714), mean III-V inter-peak ABR latencies (p-value=0.691) and mean I-V inter-peak ABR latencies (p-value=0.483).

Conclusion: Menopause does not cause abnormal results in auditory brainstem responses.

Keywords: Estrogens, Evoked potentials, Menopause, Progesterone

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Introduction

Reproductive hormones have been implicated in gender differences in sensorimotor and cognitive functions in animals and humans (1). Exposure to reproductive hormones during development leads to sexual dimorphism in central nervous system structures (2). This may be the underlying cause for gender differences and may also affect the auditory system (3-7).

Estrogen may influence the auditory system at different levels. The presence of the receptors in the spiral ganglion and outer and inner hair cells, suggests that estrogen may influence the auditory transmission, while the receptors in the stria vascularis may affect fluid electrolyte balance in the cochlear fluids (8,9). Estrogen has a protective role on auditory function, in conjunction with its neuroprotective effect. It has been observed that the decrease in estrogen levels, *e.g.*, after menopause or in Turner's syndrome, is associated with an increased frequency of neurodegenerative disorders (10). One mechanism of this protective effect could be based on the "genomic" (steroid hormone actions can be delayed in onset and prolonged in duration and involve gene expression and thus described as a genomic effect action of estrogen on its alpha and beta, possibly membrane receptors, as a regulator of the electrical activity of neurons, promoting synaptogenesis and the expression of nerve growth factors. Another proposed mechanism would implicate estrogen as a free radical scavenging antioxidant (11).

Progesterone is a precursor to other steroid hormones and acts as a neurosteroid. Specific progesterone receptors have not been identified in the in the auditory system, but progesterone may cross-react with other steroid receptors present in the cochlea or more proximal areas of the auditory system (12). Progesterone and its metabolites may also influence the auditory system through its interaction with the steroid binding sites on GABA-A receptors acting as a GABA-A agonist, which are present throughout the auditory system. Progesterone was found to decrease 5-HT (5-hydroxy tryptamine) levels and this may affect auditory processing indirectly (13).

The higher level of estrogen during the follicular phase of ovarian cycle is also associated with a rise in other hormone levels. The basal adrenocorticotropic hormone (ACTH) plasma level seems to rise in the late follicular phase possibly due to the enhancing effect of estrogen on corticotropin releasing factor gene transcription in the hypothalamus. The rise of ACTH during the late follicular phase is not related to higher free cortisol level, due to estrogen induced changes in corticosteroid binding protein levels (14). The lower level of free cortisol may affect the physiological response to stress during this phase of the menstrual cycle. The enhancement of vasopressin secretion is possibly due to estrogen, which was found to increase vasopressin levels in some women in the pre-menstrual period of the menstrual cycle and may also impact the fluid balance in the cochlea and thus affect the auditory function. The level of endorphin peaks 2–4 days before ovulation followed by a dip in post ovulation levels and then there is a gradual rise again during the late luteal phase, about 24 *hr* before the next menses. Women with polycystic ovarian disease and amenorrhea have levels of endorphin lower than in normal women (15).

There is also evidence that estrogen stimulates opioid receptor expression and stabilizes the levels of endorphins that tend to decrease after menopause. This may be associated with mood changes that can be helped by estrogen treatment, which increases endorphin levels in plasma (16). Estrogen also affects mood by facilitating the function of enkephalin that is also important for reproductive behavior (17).

Treatment with both estrogen and progesterone reverses the effect of estrogen alone on endorphin levels in the pituitary, and increases the levels of endorphin in the hypothalamus (18). The fluctuation of hormones during the ovarian cycle may potentially lead to fluctuation in auditory function and other sensory processes. The auditory system may be more sensitive during the peak of estrogen circulation due to its excitatory and protective effect in the central nervous system. Correspondingly, the low levels of hormones during the pre-menstrual phase may relate to less sensitive auditory function (19). The fluctuation in hormones affects higher areas of auditory processing and thus leads to changes in auditory thresholds, similar to the findings documented in other sensorimotor and cognitive functions (20).

It is expected in postmenopausal women due to decreased blood levels of sex hormones changes in

the function of the auditory system and the Auditory Brainstem Responses (ABR). Therefore, the objective of this study was comparison of mean inter-peak ABR latencies in post-menopausal women compared to non-menopausal women.

Materials and Methods

This cross-sectional study was conducted from 2019 to 2021 and consisted of 60 women (case group) in the age range of 45-55 years, who were post-menopausal and had normal hearing. The menopausal condition of the case group was confirmed based on the diagnosis of the gynecologist. The control group included 60 non-menopausal women in the age range of 45-55 years with normal hearing.

The inclusion criteria consisted of the age range of 45-55 years, intact tympanic membrane, the lack of middle and the external ear problems, normal tympanogram, normal ipsi and contralateral acoustic reflexes, normal hearing function based on pure tone audiometry, speech reception threshold, and speech discrimination score in noise.

Exclusion criteria were hysterectomy, history of estrogen use and hormonal therapies, ovarian cysts and any type of ovarian and uterine cancers, a variety of syndromes, any type of hearing loss, and inflammatory lesions of the middle ear.

Ethical considerations

In this research, privacy and personal information were reserved and respected. There was no action that was in conflict with their safety, health and well-being, and they were excluded from the survey at any stage that the individuals concerned were reluctant to continue to cooperate.

Checking the calibration of audiologic system was done on a daily basis to ensure that all instruments produced at the specified level and frequency. In each step of the evaluation, when the procedure was completed for the one test, subjects were given a short break and the whole procedure repeated for another.

For the impedance metric tests, middle-ear pressures and acoustic reflex measurements were made using Homoth tym4000 M and TDH-39 earphones. The middle-ear pressure between the limits of ±50 dapa was evaluated. The values that were out of this limit were omitted from the analyses (21). IPSI and contralateral acoustic reflexes were evaluated at 500-4000 *Hz* (22). Subjects' air conduction hearing thresholds were measured, using standard earphones (TDH-39) at 250–8000 *Hz*. Bone conduction hearing thresholds were measured using 60273 vibrators (Oticon, Denmark) at 0.5–4 *kHz* (23). The audiometer was calibrated using 4152 artificial ears with a Larson Davis (U.S.) sound level meter.

Subjects' speech reception thresholds were assessed using a two-syllable word list. Speech recognition was tested using a monosyllable, phonetically balanced word list developed in our university. The uncomfortable loudness level was also determined to detect hyperacusis.

ABR to the click stimulation was tested (Labat Epic-plus), with non-inverting electrode placed at the high forehead and inverting electrode on ipsilateral mastoid and ground electrode on contralateral side. Electrode impedances were roughly equivalent and were < 5 *k*Ω at the start of the test. Responses to 2000 stimuli were averaged (rate of 11.1/s). Responses were filtered from 70 to 3000 *Hz* (24).

Statistical analysis

All analysis was done by means of the statistics software SPSS 17. Data were expressed as mean ± standard deviation. Kolmogorov-Smirnov test was used for evaluation of normal test distribution. The mean of the variables that had a normal distribution was compared by independent t-test. p-value of < 0.05 was considered to indicate statistical significance.

Data analysis

All analyses were done by means of the statistics software SPSS 17. Data were expressed as mean ± standard deviation. Kolmogorov-Smirnov test was utilized for evaluation of normal test distribution. The mean of the variables that had a normal distribution was compared by independent t-test. p-value of < 0.05 was considered to indicate statistical significance.

Results

In this study, based on pure tone audiometry test, the hearing thresholds of both groups were better than 15 *dB* Hearing level (HL). No abnormal findings were detected in tympanometry and otoscopy examinations, ipsi and contralateral reflexes were

Table 1. Mean and standard deviation of the study population (Case ears=120, Control ears= 120) based on age

Sample	Mean	Min	Max	Standard deviation	p-value
Case	49	45	55	2.67	0.912
Control	47	45	53	1.96	

Tale 2. Mean and standard deviation of the study population (Case ears=120, Control ears=120) based on the auditory brainstem responses and distortion product otoacoustic emissions

Test	Ear		Mean	Min	Max	Standard deviation	p-value
I-III inter-peak interval ABR latency	Case	Right	2.49	1.51	2.21	2.12	0.714
		Left	2.60	1.49	2.68	2.78	
	Control	Right	2.32	1.54	2.81	0.99	
		Left	2.20	1.48	2.73	1.12	
III-V inter-peak interval ABR latency	Case	Right	2.61	1.53	2.81	2.54	0.691
		Left	2.73	1.50	2.98	2.96	
	Control	Right	2.85	1.55	2.59	1.80	
		Left	2.90	1.57	2.88	1.95	
I-V inter-peak interval ABR latency	Case	Right	5.10	3.04	5.02	1.53	0.483
		Left	5.33	2.99	5.66	2.1	
	Control	Right	5.07	3.09	5.40	3.25	
		Left	5.10	3.05	5.61	3.88	

observed, and speech discrimination scores in the presence of white noise were also normal.

As can be seen in table 1, the mean age of the case and control groups are not significantly different from each other (p-value=0.912). The I–III and III–V interpeak latencies of ABR were not significantly longer in post-menopausal women (Table 2)**.** Based on independent t-test, all differences between two groups were not significant, as follows; Mean I-III inter-peak ABR latencies (p-value=0.714), mean III-V inter-peak ABR latencies (p-value=0.691), and mean I-V inter-peak ABR latencies (p-value=0.483).

Discussion

In our study, it was observed that there were no significant differences between the means of inter-peak ABR latencies, which confirmed the absence of lesions in the auditory nerve and the nerve fibers of the brainstem. Therefore, the decrease in the estrogen during the menopause was not to the extent that causes pathological conditions for our case group. The important point is that menopause is a normal condition in women and is not a disease. Given that estrogen levels are much lower in men than in women, it can be concluded that the blood level of estrogen in post-menopausal women reaches a similar level to men. Evidence in this regard is as follows:

Sexual dimorphism has been noted in auditory structures, such as the cochlea in females which may have a larger number of outer hair cells and is shorter than the cochlea in males (3). The sexually dimorphic structure of the serotonergic system as mentioned above, may also modulate neural transmission in

the auditory brain stem and cortical structures (7). The differences in reproductive hormones during development and in adulthood may explain gender effects in auditory function, specifically the theoretical possibility that auditory function is "better" in females than males due to the excitatory and protective effects of estrogen (3-7).

It has been reported that adult females have more sensitive hearing in higher frequencies compared with males (3) which is also noted in carefully screened populations for noise exposure (4). It was also observed in school-aged children, that girls tend to have lower audiometric threshold compared to boys, however the difference was not statistically significant (3). Females tend to have OAE with larger amplitudes compared with men (5) and are more likely to have recordable spontaneous OAE; 75% of females compared with 58% of males. OAE are thought to originate from the outer hair cells reflecting cochlear function and are associated with good hearing sensitivity (3). The gender difference is also seen in neonates and older children which may be due to prenatal hormonal exposure (6). The excitatory effect of estrogen and sexual dimorphism in the central nervous system and auditory system may affect the neural transmission in the auditory brainstem leading to gender differences in ABR. Female adults were found to have shorter ABR wave latencies and larger wave V amplitude compared with males, but to a lesser extent in older children (7).

It is possible that the auditory system in some women is more sensitive to the fluctuation of hormones. Maybe that is why our results are not the same as some of the studies, which suggest that ovarian hormones may have an effect on synaptic transmission in the auditory brainstem, as below;

Souaid and Rappaport described a case of a 45-year-old woman who had bilateral hearing loss with the onset of menses with right ear blockage and tinnitus that improved later on during the cycle. They also reported that she had an abnormal ABR recorded in the middle of her ovarian cycle (prolonged III–V inter-peak interval on the left and delayed wave V with prolonged I–V inter-peak interval on the right). She was treated with diuretics, which improved her symptoms, and the ABR results of the right ear but the ABR results of the left ear were the same as before, and her hormonal profile was within normal limits (25).

Some studies reported that Hormone Replacement Therapy (HRT), in postmenopausal women, brings ABR latencies closer to the values observed in pre-menopausal women (26). Caruso *et al* (27) reported that ABR latencies were also found to be significantly shorter in postmenopausal women after the use of different forms of HRT (28). Cooper *et al* stated that the effect of HRT in post-menopausal women on ABR latencies is similar to what is seen in females with premature ovarian failure (29). Caruso *et al* reported that shorter ABR latencies during the periovulatory phase of the cycle may suggest that the high estrogen level is associated with shorter ABR latencies and higher level of estrogen may alter the speed of sensory neurotransmission in the brain stem by modulating glutamate transmission (27).

Another explanation may be that a fluctuation in hormones affects higher areas of auditory processing and thus leads to changes in auditory thresholds, as follows; the onset of age-related hearing losses later in women compared with men and seem to coincide with the menopause (30). Thus, further larger studies on the effect of the ovarian cycle on auditory functions are required to clarify the results found in the previous studies.

A few studies explored the possible association of hearing loss assessed by pure tone audiometry in post-menopausal women; Kim *et al* suggested that a lower level of serum estradiol impedes hearing sensitivity in post-menopausal women (31). Kilicdag *et al* expressed that post-menopausal women using estrogen therapy had better pure tone thresholds compared with those who did not use it (32). A recent study by Hederstierna *et al* evaluated the hearing thresholds in a group of women around the time of menopause and found that 40% had some degree of hearing loss. They reported that a subgroup of women who were not using HRT had a tendency of poorer hearing threshold levels compared to pre- and peri-menopausal and postmenopausal women who were using HRT (33). These studies suggest that HRT and in particular estrogen therapy may have a beneficial effect on hearing sensitivity.

The studies that measured hormone levels and ABR produced conflicting findings. In studying the effect

of menopause on the auditory system, age is an important consideration. Murphy and Gates reported that the onset of age-related hearing loss seem to coincide with the menopause (34). It is important to differentiate the effects of age and estrogen on auditory system. Wharton and Church stated that gender plays a significant role in ABR wave latencies (35). The different results in previous studies, maybe were due to the lack of exactly separation of these two factors. Whereas, we removed aging distorting factors of our research; two groups of women had normal auditory functions from the surface of the outer ear to the cerebral cortex; we considered the normality of speech discrimination in the presence of noise and observation of ipsi and contra reflexes.

Conclusion

Menopause does not cause abnormal results in auditory brainstem responses.

Acknowledgements

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