Sex as a source of variance affecting auditory evoked potential

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As a noninvasive measure of physiological integrity of auditory pathway, auditory evoked potential (AEP) has gained popularity globally. Baseline reference values specific for each setup demand normative AEP study, in which sex is one of the confounding factors affecting it. We tried to review studies conducted to correlate sex and AEP among various age groups with exploration of various explanations for it and the extent to which they are significant.

Keywords:
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Introduction

Following breakthrough description by Jewett and Williston in 1971, auditory evoked potential (AEP) has grown as a useful, noninvasive, objective, neurophysiological diagnostic tool to evaluate the functional integrity of the neural pathway [1,2] concerned with one of the special senses, hearing. It has been studied in large groups to lay normative baseline data and in patients with a variety of neurological diseases. AEP includes brainstem auditory evoked potential (BAEP) and cortical auditory evoked potential (CAEP) that dissect information on nerve conduction in response to sound stimulus along brainstem and cerebral cortex, respectively.

AEPs are now widely used in audiology, neurology, neonatology and anaesthesiology [3]. However, like each test based on physiology there is existence of variables that affects the results of AEP waveforms recorded and ultimately the interpretation or diagnosis made. These variables can be related to stimulus, recording parameters and subject. The first two out of the three can be nullified by using universal guidelines existing for them and by standardization of protocol, whereas the latter still remains a confounding factor to be taken into consideration, of which age and sex are the two parameters affecting AEP and needs to be studied. Women have, on average, greater hearing sensitivity compared with men. Behavioural, morphological and physiological sex-related differences have been demonstrated to exist throughout the auditory system in humans [4–7]; therefore, sex bias can be present in evaluation of the same in terms of nerve conduction. This article summarizes research works dealing with the effect of sex-related differences on AEP.

Discussion

Basis from birth to puberty

Sex-related differences can be studied along the developmental progression of an individual as a whole. In general, women have shorter latencies and larger amplitudes of AEP waveforms compared with men. Sex-based AEP difference is evident even in full-term newborns in interpeak latencies (IPL) [8]; it is absent in preterms [9], being explained by the fact that head size, which is a measure of brain maturation, is absent in preterms. A study conducted on children aged 2–720 days showed a statistically significant difference in wave III and V latency values and in III–V and I–V intervals between boys and girls [10]. A study showed that the functional maturation of oscillatory auditory networks reflected by a progressive developmental increase of synchronization is accelerated in girls relative to boys between 7 and 10 years of age [11]. An event-related potential study demonstrated that boys produced larger N1 amplitudes compared with girls and that boys produced longer P2 latencies compared with girls, but only in older children [12]. Studies conducted on pubertal age group girls demonstrated evidence of latency difference [13,14].

Postpubertal sex-related differences in AEP

In general, for BAEP latency, amplitude and IPL differences are observed more consistently in late components of waveforms [10,15,16], whereas CAEP early components [17–20] show sex-related difference mainly in latency but not in amplitude. Sex-dependent amplitude difference is not observed much after the age of 25 years [21]. However, the male disadvantage for AEP latency persists in college students [22], young adults [15,18,23–26], middle-aged individuals [15,25] and even in the old-age group [25]. Latency prolongation when responding to auditory stimulus in

male population may thus help to explain the higher incidence of reading impairment in male population compared with female population [21].

Indian studies with sex bias of AEP

There are few studies published on normative AEP values in India. A North Indian study suggested no sex-related difference in BAEPs between 3 and 13 years of age [27], but in the age group 16–45 years it was found evident in another study [28]. In late teenagers of west India (age 15–19 years) smaller latency difference and significant IPL difference were observed, which became insignificant after head size or BMI normalization [14]. A recent North Indian normative study showed significant IPL differences between sexes in individuals more than 15 years of age, which was not evident for mere latencies [15]. Another South Indian work revealed that in the age group of 18–40 years, significant latency and IPL differences were observed between male and female population for all waves [26]. However, most of the normative studies have focussed on BAEP and a few on CAEP. There is a need of a study including all age groups and both sexes, as in infants, children and young individuals of India, uncertainty exists about what is the age of onset for sex-related difference to begin.

Head size as a basis of sex bias in AEP results

Of various possible explanations put forward for explaining this sex bias of AEP, head size, which is a measure of neurological length of auditory pathway, seems to be most commonly reported by researchers. Head size that reflects brain size [29] is one of the important factors for the basis of sex-related differences in BAEP latencies, which is given in full-term newborns, infants, children and young adults [15,24,26,30–33]. There is still a contradiction because a few have found that latency differences were reduced after taking comparable head size [14,34,35] but others did not [33,36]. It is proven that head size does not play a major role in the sex-related differences in interpeak intervals [13]. One study has pointed that head size affects latency of wave V and IPL I–V more [16], and another has suggested that this can be neutralized by taking ratio of amplitude of wave V–I [36]. It has been suggested that this functional–anatomical correlation is too weak to be considered as valid and the only reason [36,37]. In recent times, it has been found that brain volume is not related too strongly to AEP and that head size is not the sole cause for results observed as sex bias in AEP [38].

Physiological explanations of sex bias in AEP results

Sex hormonal difference is also a significant causative factor for the difference in question because of the following reasons:

(a) Stronger click-evoked otoacoustic emissions exist in healthy, normal-hearing young women compared with men [6];
(b) Women demonstrate more acute sound sensitivity compared with men [39];
(c) These differences are reduced during menopause [40], in women taking oral contraception [41] and those who have a male twin [42], which suggests a role of hormones, including oestrogen, in improving auditory function in women [6];
(d) Oestrogen enhances synaptic transmission improving neural conduction [43];
(e) Oestrogen replacement treatment can decrease auditory brainstem response (ABR) intervals [44] and certain latencies of the MLR in postmenopausal women [45];
(f) Prolonged AEP intervals in men have been attributed in part to the degree of exposure to androgens during prenatal development [6,46];
(g) Certain AEPs can shift in the male direction in women using oral contraceptives [17,41]; and
(h) relevant auditory structures are altered during prenatal development, possibly on exposure to androgens [8].

Hormonal differences and head sizes have been demonstrated as causative factors for sex-related difference in ABR result [47].

Neural pathway and its development as a cause of sex bias in AEP results

The neural pathway and its development are also a contributory factor to sex-related differences. Men and women differ in their cochlear size, with women having shorter cochlear ducts compared with men, resulting in shorter cochlear travel times in women [48]. The travel time difference is also affected by the greater stiffness of the female basilar membrane resulting from its shorter length and may contribute to women having earlier latencies relative to men in the speech ABR [49]. Moreover, these peripheral differences may be because of differential activation of the oliviocochlear system, suggesting sex-related differences in efferent modulation [6,49]. Imaging studies have indicated that male and female cortices process acoustic stimuli differently. For example, functional MRI studies have shown stronger activation of cortical language processing areas in girls, as compared with boys, throughout development [50]. Overall, girls exhibited shorter P_{300} latencies and smaller P_{300} amplitudes compared with boys, suggesting more efficient information processing [13]. Between the sexes, significant differences exist in the click-evoked ABR, a response predominately representative of high-frequency information suggesting that

subcortical response to a complex auditory stimulus is faster in female population for high-frequency stimuli compared with male population.

Other minor causes of sex bias in AEP results

In women, AEP does not vary much with anovulatory cycle [51], menstrual cycle, [52] and pregnancy, and there is documentation that handedness [19,23] and heterosexuality [17] are not significant sources of difference. Women can have a slightly higher body temperature compared with men [48], and this factor has been considered in the past as a possible basis for the sex-related difference in AEPs. However, a global difference in body temperature seemingly is inadequate as an explanation for the fluctuating pattern of sex-related differences seen.

Conclusion

Sex has a definite individual effect on AEP results evident from infancy, which persists up to late 50's and perhaps beyond. Head size is a factor behind latency prolongation in men compared with age-matched women but not the sole one, and sex hormonal difference is an equally contributory cause for this sex-related difference starting from prenatal life and persisting throughout adulthood. Recent evidences in sex-based difference of cortical and subcortical processing are further adding to the complexity, and ultimately these multiple factors contribute as a whole. Variable results across the globe suggest region-specific and setup-specific normative data to be established with fairly large sample, especially in India, giving due importance to physiological confounding factor like sex. Using norms of these subjects' related parameters along with the use of standard protocol will allow optimum utilization of AEP as one of the reliable neurodiagnostic tool, whose results can be universally accepted.

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Conflicts of interest

None declared.

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