Auditory brainstem responses in children with autistic spectrum disorder.

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Abstract

Background:

Autism spectrum disorder is a heterogeneous behavioral disorder characterized by qualitative deficits in social communication and interaction and restricted, repetitive behavioral patterns, activities, and interests. The assessment and management of autism spectrum disorder (ASD) is complex and therefore requires continuous efforts for developing evidence-based guidelines for the screening, diagnosis, and treatment of ASD. This research aims to study auditory brainstem response (ABR) in autistic children as a potential biomarker that could detect autism during early childhood.

Patients and methods:

The study was conducted on 60 preschool children comprised 11 females and 49 males who were recruited from the autism center and the pediatric neurology ward who met the DSM-IV criteria for autism in the Pediatric Hospital. Those with hearing , epileptic syndromes, psychotic illness, or other affective disorder were excluded from the study. Their mean age was 4.5±1.17 years. Another 50 (40 males and ten females) age- and gender-matched normally-developed children serve as the control group.. Childhood Autism Rating Scale used , audiological studies were performed with emphasis on ABR by a consultant of audiology.

Results:

Statistical analysis was done on the results and the study showed Wave V latency and I-V IPL of the brainstem auditory evoked potentials were significantly prolonged in both ears of autistic children when compared to the control group. The III-V IPL of the right but not the left ear was prolonged in patients with autistic children as compared to the controls. None of the wave latencies or IPL were associated with gender or severity for both right and left ears.

Conclusion:

There are distinct changes in BAEP in ASD children, especially the abnormal prolongation of conduction time, suggesting that ASD children may have brainstem dysfunction ,can be part of a generalized neurological dysfunction process that explains a change in the social, cognitive, language which are part of autistic behavior.

Key word :autism spectrum disorders; brainstem auditory evoked potential ; Childhood Autism Rating Scale ; Diagnostic statistical manual of American psychiatric association; Interpeaks latency(IPL) .

Introduction:

Autism spectrum disorders

Autism spectrum disorder (ASD) refers to a lifetime, generally stable condition of a group of pervasive neurodevelopmental disorders that involve moderately to severely disrupted functioning regarding social skills and socialization, expressive and receptive communication, and repetitive or stereotyped behaviors and interests (1; 2).

It is known as a "spectrum" disorder because there is wide variation in the type and severity of symptoms people experienced. The broad term encompassing autistic disorder, Asperger disorder/syndrome, and pervasive developmental disorder not otherwise specified. These disorders all share common features of impaired social relationships, impaired communication and language, and stereotypic motor mannerisms or a narrow range of interests (3).

Epidemiology

The most recent global burden of disease estimates revealed 62.2 million people with ASD around the world in 2016 (4). The prevalence has been steadily increasing over the past two decades, with current estimates reaching up to 1 in 36 children. Community-based prevalence rates for ASD in the general population show considerable variation across studies, though recent systematic reviews and large-scale epidemiological research estimate rates of between 0.7-1.1% (5; 6;7). Similar prevalence estimates have been reported in adults (8). Over the past decade or so, studies across the world have estimated an increase between 50% to over 2,000% in cases of autism (9).

Additionally, the prevalence of autism is significantly higher in people with moderate to profound intellectual disability comorbidity is common (e.g. more than 50% may present concurrent physical or mental conditions) (10; 11).

Autism spectrum disorder seems to affect more male than female individuals with approximately 4 affected males for every 1 affected female (12;13). Intelligence level affects this sex ratio: males are substantially over-represented among high-functioning cases, and males and females are more equally represented among cases with severe intellectual disability. They reported that girls showed more social and communication and had fewer repetitive behavior symptoms (14)

Pathophysiology & Risk factors

The exact pathomechanism of ASD is not known so far while several factors have been implicated in its pathogenesis of autistic disorders. The mechanism that leads to ASD is very complex, involving genetic, epigenetic, immune, and environmental factors that could act in different proportions, at different developmental stages (prenatal, perinatal, or postnatal) and on different pathways (15).

From the epidemiological point of view, the identification of the exact timing of action of each environmental factor, as well as its consequences in the neurodevelopmental pathways, remains elusive. Nevertheless, it is now possible to establish some differentiation among risk factors that can assist in developing detection and a personalized follow-up of populations at higher risk for ASD (16).

The general prototype consists of an initial systemic dysfunction, such as immune dysregulation, inflammation, impaired detoxification, or oxidative stress in an individual with a genetic predisposition. ASD may arise due to the harmful action of environmental factors that lead to neuroinflammation and abnormal brain development.

Environmental factors involved in autism determinism could be very diverse and include classical extrinsic factors (toxicants, environmental pollutants, medications, food additives, electromagnetic fields, and even social influences), maternal disorders or lifestyle factors, as well as intrinsic factors (hormones, inflammatory mediators, microbiota and other biological molecules that make up the microenvironment around the developing fetal or neonatal brain (17).

Sensory symptoms

Over 96% of children with ASD report hyper and hypo-sensitivities in multiple domains. Similar to the wide range of spectrum severity found for communication and social deficits, sensory behavioral differences also range from mild to severe, and these behavioral differences can endure through adulthood (18; 19; 20).

Sensory hypersensitivities or hyposensitivities to the environment are also highly prevalent in children with ASD (21). Sensory symptoms can be broken down into three patterns: hyperresponsiveness which involves overreactions to the sensory environment (e.g. covering ears to the sound of someone singing), hyporesponsiveness which denotes under-reactions to the sensory environment (e.g. not turning to a loud sound, and sensory seeking which includes a prolonged visual inspection of toys or repetitive touching of objects (22).

Recent estimates of the prevalence of sensory symptoms of people with ASD range from 69% to 93% in children and adults (23) and were recently added as a diagnostic criterion of ASD in the DSM-V (2).

The brainstem has long been suggested to be a key region of importance for autistic symptomatology and also for sensory modulation. Using MRI and proton spectroscopy, brainstem volumetric reductions of grey and white matter volumes were found in children with ASD. The findings were taken to support the existence of a disturbance in the brainstem circuitry associated with the sensory dysfunction observed in autism. These support the possible involvement of the thalamus in the pathophysiology of ASD and the sensory abnormalities observed in this patient group (24).

Persons with autism have a delay in or a lack of language development, which they do not compensate for by using other nonverbal means of communication. About half of the children with ASD never develop speech. There is great variation among the children who do. Some only use single words. Others use many words and speak correctly, but mostly repeat stock phrases or things others have said regardless of the situation. A smaller number have a well-developed and spontaneously spoken language (25).

Auditory sensory processing

As language deficits are a core feature of ASD, the study of auditory processing is essential to consider the roots of ASD as well as to theorize rational interventions. One way of measuring the flow of auditory information processing is through the traditional brainstem auditory evoked potentials (BAEPs).

Consequently, while brainstem abnormalities do not appear sufficient to explain the deficits for all individuals on the autism spectrum, there is literature suggesting measurable differences in early auditory pathways, especially with increasingly complex stimuli. Understanding the nature of this fundamental step in the auditory sensory stream is crucial because the ability to acquire and analyze a variety of incoming sounds forms the foundation for language and communication In general, the neurophysiologic study of auditory processing in ASD does suggest atypical neural activity as early in the processing stream as the primary auditory cortex. However, as Whitehouse and Bishop suggest, these differences may be a result of top-down inhibitory processes mediating encoding and early sound processing (26).

Severity score of ASD

Recent studies have suggested that autistic symptoms are continuously distributed in the population forming a broad spectrum as the disorder may take many forms from mild-moderate-severe with a variety of impairments. This increasing heterogeneity of the disorder can cause difficulty in measurement and assessment. Measures should be able to quantify subtle differences in the degree of impairment across the spectrum and alert clinicians to the severity of symptoms, including those that may be sub-threshold (27).

Currently, biological diagnostic markers are not available and diagnosis rests on careful examination of the child. A standard psychiatric assessment should be followed, including interviews with the child and family and a review of records and historical information. Observation and assessment should include the core symptoms of ASD and according to DSM-5 which specifies that persons with ASD must meet all three social criteria (i.e., deficits in social-

emotional reciprocity, deficits in nonverbal communicative behaviors, and deficits in developing, understanding, and maintaining relationships).

Various instruments for the assessment of ASD have been developed as seen in Table 1-3. As a practical matter, all these instruments vary in their usefulness for usual clinical practice and some require specific training (28).

Among all these scales and assessments, Childhood Autism Rating Scale (CARS) is promising as a diagnostic measure because of its simplicity, conceptual relevance, high concordance with DSM -5 diagnosis of autism, acceptability, cost-effectiveness, utility among different populations, and strong psychometric properties when validated (29).

The CARS is a 15-item behavior-rating scale designed to detect and quantify symptoms of autism as well as to distinguish them from other developmental disabilities. Each item on the CARS is scored on a Likert scale, from 1 (no signs of autism) to 4 (severe symptoms). The maximum CARS score is 60, and the cut-off for a diagnosis of autism is 30. Children with scores of 30.5 to 37 are rated as mildly-moderately autistic, and 37.5 to 60 as severely autistic (30).

The scale assesses behavior in 14 domains that are generally affected by severe problems in autism, plus one general category of impressions of autism, to identify children with autism, as differentiated from the other developmental disorders. The 15 items in the scale are: relating to people; imitative behavior; emotional response; body use; object use; adaptation to change; visual response; listening response; perceptive response; fear or anxiety; verbal communication; non-verbal communication; activity level; level and consistency of intellective relations; and general impressions.

The examiner assigned a score of 1 to 4 for each item: 1 indicates behavior appropriate for age level, while 4 indicates severe deviance concerning normal behavior for the age level. The scores for The single items are added together into a total score, which classifies the child as not autistic (below 30), mild or moderately autistic (30-36.5), or severely autistic (above 36.5) (29).

Brainstem auditory evoked potentials

Auditory evoked potentials (AEP) can be used to trace the signal generated by a sound through the ascending auditory pathway. The evoked potential is generated in the cochlea, goes through the cochlear nerve, through the cochlear nucleus, superior olivary complex, lateral lemniscus, to the inferior colliculus in the midbrain, on to the medial geniculate body, and finally to the cortex (Figure 1) (31).

The BAEPs are small AEPs that are recorded in response to an auditory stimulus from electrodes placed on the scalp. AEPs serve for the assessment of the functioning of the auditory system and neuroplasticity , They can be used to diagnose learning disabilities in children, aiding in the development of tailored educational programs for those with hearing and or cognition problems (32).

It consists of a series of peaks that occur within 10 msec after an abrupt stimulus such as a click. Waves I and II originate from the vestibulocochlear nerve while waves III–V depends on the neural functioning of the cochlear nucleus through the lateral lemniscus (33).

Subjects & Methods

A prospective case-control study was conducted at the Autism Center, Baghdad Teaching Hospital, Pediatric Hospital, Medical City for the period from 12th Dec. 2019 to 1st Jun. 2021.

Subjects

The study was conducted on 60 preschool children comprised 11 females and 49 males who were recruited from the autism center and the pediatric neurology ward in the Pediatric Hospital and met the DSM-IV criteria for autism. Another 50 age- and gender-matched normally-developed children who do not fulfill the criteria of any pervasive developmental disorder serve as the control group.

The autistic children were excluded from the study if they had any motor, auditory Impairment, inborn errors of metabolism, epilepsy, psychotic illness, or other affective disorder ,chronic medical or neurological disorder, or taking medications during the period of study.

Methods

All the studied children were subjected to the following:

History and clinical examination

Full physical and medical history was taken; patient demographics were registered. Again, physical, neurological, and psychiatric examination for clinical assessment of ASD and its severity according to DSM-IV criteria was also done.

Brainstem auditory evoked potentials

The BAEPs were performed using Otometric IC5, Chartr EP 200 (Germany) in a darkened quiet room while the child is asleep. The BAEP recordings were performed in a quiet room at a constant room temperature of 30^{o}C. During the procedure, an abrupt auditory stimulus (click) generates sequentially several components identifiable in the averaged EP recorded over the scalp. Of these are the early components that occur within the first 8-10 msec following click stimulus due to activation of the cochlear nerve and brainstem auditory structures.

Electrode placement

Electrode application followed the International 10/20 System of Electrode Placement with one channel setting. The surface electrodes are placed for BAEP recordings and secured by electrolyte paste or collodion as follows:

a) Two electrodes at each ear lobule (A1 and A2) as active and reference.
b) A ground electrode is placed commonly at the mid-forehead (Fz) location.

Stimulation

The electrode impedance was maintained below 5 kΩ. Single polarity (rarefaction) clicks were presented monaurally through earphones at a repetition rate of 27.1/second. Hearing thresholds were searched for at a starting level of 70 dB; if present, then a 20 dB stepwise reduction, and if absent, a 10 dB stepwise increment was ensured.

Recordings were filtered online with a 100-3000 Hz band-pass filter. The stimulus type is 100 μsec broadband clicks.

Two thousand responses were averaged for each record, each ear was tested separately and two replications were performed on each subject. The non-stimulated ear was masked by the noise of 30-40 dB < click intensity used to stimulate the ear. Then other BAEPs waves are obtained at 40 dB for all children.

Statistical analysis

All statistical analyses were performed using SPSS statistical software, version 25 (IBM Corporation, USA). Quantitative variables were subjected to a normality test (Shapiro Wilk test).

Variables with normal distribution were presented as mean ± standard deviation (SD) and analyzed with Student t-test (for two groups comparison) or analysis of variance (ANOVA) (for more than two groups comparison). For all tests, a significant level of statistics was considered when $p<0.05$ (34).

Results

One hundred and ten children were enrolled in this study, 60 diagnosed to have ASD (49 males and 11 females) and 50 normally-developed children (40 males and 10 females). No significant difference was noticed between the two groups regarding gender ($p = 0.825$). Also, no significant difference ($p = 0.390$) was found between the age of children with ASD (4.5±1.17 years) and the normally-developed children (4.68±0.97 years).

BAEPs data

Analysis of BAEPs parameters revealed that there was no significant difference in wave I latency and the I-III IPL of both sides between the children with ASD and controls. Wave III latency was

significantly prolonged in the right but not the left ear of patients as compared to the controls ($p = 0.009$). Wave V latency and I-V IPL were significantly prolonged in both ears of children with ASD ($p < 0.001$) when compared to the control group. Finally, the III-V IPL of the right but not the left ear was significantly prolonged ($p = 0.002$) in patients with ASD as compared to the controls (Table 1).

Gender and BAEPs data in children with ASD

None of the wave latencies or IPL of all components was associated with gender for both right and left ears (Table 2).

Disease severity score and BAEPs data

None of the wave latencies or IPL of all components was associated with the disease severity score for both ears (Table 3).

Discussion :

Language and learning disability disorders associated with ASD lead parents, pediatricians, or general practitioners to reference these children to consultation (35). Generally, the main complaint of the parents is the delay of spoken language. There are also divergent responses to sounds because of an alteration in sensory processing causing atypical responses to different stimuli - hyper or hyporesponsive (36). Thus, the BAEPs is often the only test that provides us some indication of the hearing status in those with neurological and psychiatric disorders, including children with ASD, since we are dealing with children who do not cooperate, possibly due to a deficit of attention and cognitive dysfunction (37).

Given the results, in this study, there was a group effect for wave III and wave V latencies, I-V and III-V IPL of BAEPs elicited by click stimuli, for which the ASD group showed greater values than the controls. This electrophysiological evaluation provides evidence that there is a delay in auditory processing on the brainstem level in children with ASD compared to the control group which implies a role for the brainstem in autism pathogenesis. This delay in conducting the auditory stimuli through the brainstem can be explained by different mechanisms: hypoplasia of some nuclei of the brainstem, neuronal immaturity, and brain overgrowth during the first years of life that consequently will affect the length of the cochlear nerve and auditory pathways in the brainstem which leads to increase in absolute and IPL latencies in BAEPs (38; 39).

This suspected dysfunction in the brainstem, affecting the processing of sensory afferents through the auditory pathways, can be part of a generalized neurological dysfunction process that explains a change in the social, cognitive, and language, which are part of autistic behavior.

The scientific literature reports contradictory results on the BAEPs of autistic children. Some studies confirm the lack of changes in BAEPs with click stimuli in individuals with ASD (40; 41; 42,43) which is not following the findings of this study. This can be explained by sample sizes used in these studies, by the inclusion of a higher proportion of individuals with milder forms of autism, probably owing to age, and other selection differences among the samples.

However, other authors have found an increase in the absolute latencies of waves III and IV (44), an increase in the latencies of waves I and V (45), and increased latencies of wave V in the right ear and wave I in the left ear in individuals with ASD (46).

The dysfunctions observed along the auditory pathway in children with ASD have also been emphasized in other studies that observed changes in the IP intervals. One study that assessed children with ASD also found changes only in the IPL III-V in these children compared with control children (46). Other studies have also observed increases in this IPL, along with other changes like IPL I-V in children with ASD relative to typically developing controls (47;48; 49) and prolongation of IPL III-V (38) have also been observed in children with autism.

These findings corroborate the results of this study in which autistic children had a significantly longer transmission time on the brainstem when compared to control children.

Additional studies have found changes in IP intervals other than those observed in this study, such as IPL III-IV (50), and IPL I-III (51; 39).

The changes in the latency values and IPLs of BAEPs are known to reflect changes in the myelination, axon diameter, and synaptic efficacy of the auditory pathways at the brainstem level (52). Thus, the results of this study suggest that children with ASD exhibit abnormal cortical structures at the brainstem level, which impairs the conduction of neuroelectrical impulses of stimuli between the cochlear nuclei and the lateral lemniscus (53).

Although female controls have shorter IPLs, and thus their inclusion may bias IPLs to be shorter in controls and appear longer in ASD (54). It should be highlighted that all BAEPs parameters of patients with ASD in the present study exhibited a non-significant correlation with gender. Another attempt to diminish methodological bias was assumed in the present study as the patient age was older than three years to avoid the wave V maturation process (although the rest of the parameters matured by the age of two, wave V structure is still developing until 3 years of age in typically developing children (55).

Importantly, children with ASD showed a tendency toward abnormal wave III latency and III-V IPL on the right but not the left side. The tendency for this right-hemispheric abnormality in ASD children suggests a disturbance of the right hemisphere ascending reticular brainstem pathways and/or their thalamic and cortical projections, which in turn may contribute to abnormal arousal and attention. Abnormal hemispheric responses or lack of lateralization have also been described in the auditory domain (56; 57; 58).

Furthermore, there was no significant correlation between CARS scores (severity score) and the outcome of the various BAEPs parameters.. Similar findings were also reported in other studies (59; 41).

Considering the above-described findings, it can be verified that children with ASD may have a different pattern of sound transmission throughout the nervous system. The delayed onset of wave V and increased IPL III-V have been demonstrated to be the most frequent alteration among children with ASD and are suggestive of a possible change in the upper brainstem region in these individuals.

Conclusion :

1) There are distinct changes in BAEP in ASD children, especially the abnormal prolongation of conduction time, suggesting that ASD children may have brainstem dysfunction.
2) This suspected dysfunction in the brainstem, affecting the processing of sensory afferents through the auditory pathways, can be part of a generalized neurological dysfunction process that explains a change in the social, cognitive, language which are part of autistic behavior.
3) Gender has no impact on BAEPs data.

Recommendations :

As many medical centers regularly perform BAEPs tests for every neonate at the risk of hearing impairment, it is important to conduct further researches on this test to determine the risk of autism. Multidisciplinary care is important for the differential diagnosis of hearing loss, ASD, or the association between them, to ensure the most adequate intervention for each case.

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Table(1). BAEPs Parameters in patients with ASD and controls

Parameter/side		ASD (N=57) Mean±SD	Controls (N=50) Mean±SD	P-value
Wave I latency (ms)	Right Left	1.87±0.38 2.0±0.46	1.8±0.26 2.05±0.47	0.260 0.560
Wave III latency (ms)	Right Left	4.35±0.62 4.4±0.54	4.08±0.36 4.21±0.53	0.009 0.065
Wave V latency (ms)	Right Left	6.42±0.89 6.37±0.46	5.92±0.23 5.86±0.59	<0.001 <0.001
I-III IPL (ms)	Right Left	2.42±0.63 2.39±0.47	2.25±0.35 2.17±0.42	0.105 0.012
III-V IPL (ms)	Right Left	2.12±0.53 1.99±0.35	1.84±0.33 1.83±0.59	0.002 0.071
I-V IPL (ms)	Right Left	4.55±0.68 4.38±0.57	4.02±0.54 3.87±0.41	<0.001 <0.001

BAEPs = brainstem auditory evoked potentials; ASD = autism spectrum disorder; IPL = interpeak latency

Table (2) Association of gender with BAEPs parameters in children with autism spectrum disorder

Parameter		Males (N=49) Mean±SD	Females (N=11) Mean±SD	P-value
Wave I latency (ms)	Right Left	1.88±0.39 2.02-±0.51	1.8±0.34 1.92±0.12	0.533 0.539
Wave III latency (ms)	Right Left	4.39±0.62 4.43±0.53	4.17±0.59 4.26±0.61	0.295 0.323
Wave V latency (ms)	Right Left	6.52±0.59 6.37±0.48	5.98±1.65 6.36±0.4	0.069 0.847
I-III IPL (ms)	Right Left	2.47±0.64 2.39±0.46	2.17±0.55 2.4±0.54	0.183 0.923
III-V IPL (ms)	Right Left	2.11±0.52 2.0±0.35	2.15±0.6 2.0±1.36	0.832 0.990
I-V IPL (ms)	Right Left	4.54±0.72 4.37±0.59	4.55±0.47 4.41±0.48	0.979 0.846

BAEPs = brainstem auditory evoked potentials; IPL = interpeak latency

Table (3). Association of CARS with BAEPs parameters

Parameter		Mild (N=31) Mean±SD	Moderate (N=22) Mean±SD	Severe (N=7) Mean±SD	P-value
Wave I latency (ms)	R L	1.88±0.4 2.05±0.54	1.9±0.34 1.96±0.41	1.75±0.48 1.86±0.18	0.692 0.574
Wave III latency (ms)	R L	4.52±0.68[a] 4.44±0.61	4.24±0.52[ab] 4.38±0.48	3.96±0.4[b] 4.3±0.44	0.056 0.790
Wave V latency (ms)	R L	6.49±0.68 6.34±0.52	6.29±1.24 6.39±0.39	6.51±1.19 6.41±0.46	0.715 0.895
I-III IPL (ms)	R L	2.54±0.7 2.4±0.49	2.32±0.55 2.36±0.48	2.16±0.38 2.4±0.47	0.227 0.945
III-V IPL (ms)	R L	1.98±0.47 1.96±0.36	2.23±0.54 2.0±0.36	2.38±0.64 2.14±0.27	0.086 0.494
I-V IPL (ms)	R L	4.58±0.78 4.37±0.47	4.48±0.49 4.46±0.53	4.6±0.79 4.17±1.0	0.839 0.498

CARS = Childhood Autism Rating Scale; R = right; L = left; IPL = interpeak latency.

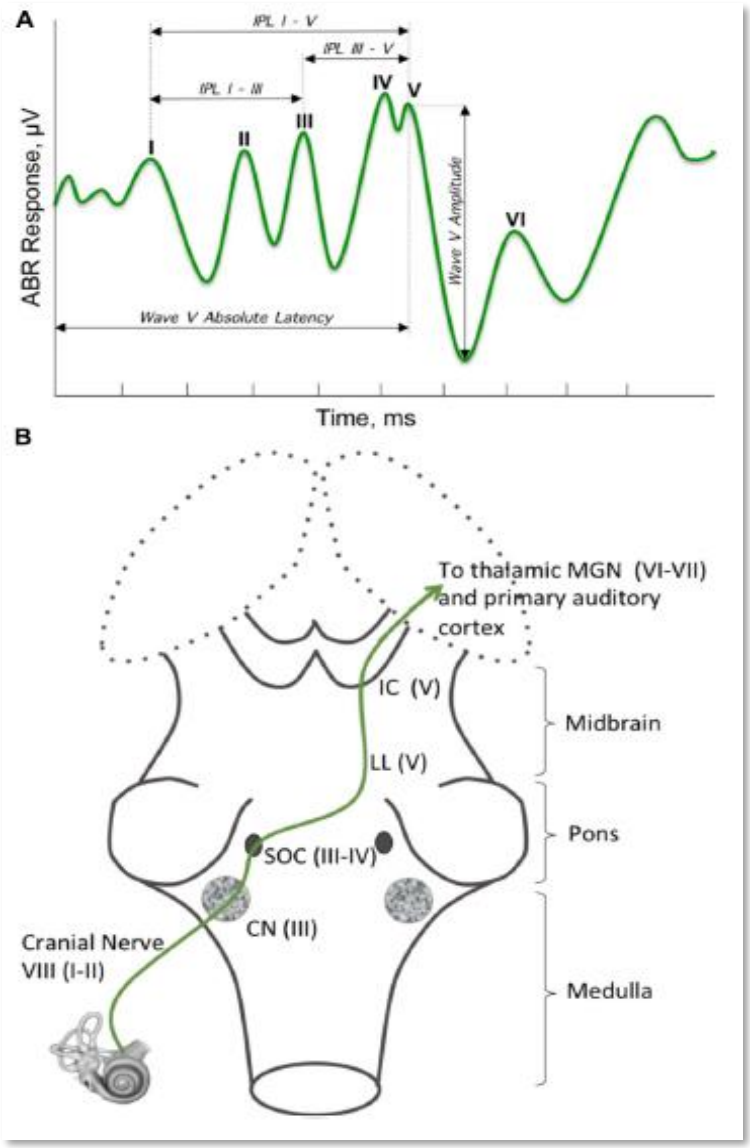

Figure (1). Brainstem regions supporting ABR. (A) ABR is a series of five to seven peaks that occur in the first 10 ms following a brief stimulus, labeled I-V, and evaluates the lower auditory system. (B) The ascending auditory signal propagates via cochlear nuclei (CN), superior olivary complex (SOC), lateral lemniscus (LL), and inferior colliculus (IC) (LL and IC are often described as the midbrain tectum), then continue to the auditory cortex through the medial geniculate body of the thalamus. Peak I originates at the distal portion of the auditory nerve (cranial nerve VIII). Signal propagation through the proximal end of the auditory nerve gives rise to peak II. Peak III is generated at the level of CN with the participation of some regions of SOC; whereas peak IV is primarily generated by the subnuclei in the SOC. Peak V is generated by neurons within the LL and IC.