NARRATIVE REVIEW

Auditory brainstem response: An overview of neurophysiological implications and clinical applications -A Narrative Review

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Abstract

Evoked Potentials are electrical potentials that occur in a group of neurons in response to stimulation of a sensory organ which can be recorded by surface electrodes. Testing evoked potentials is useful in assessing the integrity of neuronal pathways both at sensory and motor levels of neural control. Early auditory evoked potentials include cochlear and brainstem auditory-evoked potentials, popularly known as electrocochleogram, and auditory brainstem response. Evoked potential audiometry is a neurophysiogical test to assess auditory pathway function in response to auditory stimuli. Auditory brainstem response mainly assesses brainstem functions and integrity. These evoked potentials are widely used for assessment of the cochlear functions, auditory nerve and the brainstem. Most common indications for auditory evoked potentials include routine newborn hearing screening for auditory pathway deficits, detecting retrocochlear pathologies, intraoperative and intensive care monitoring, frequency-related measurement of auditory sensitivity and for diagnosing some demyelinating disorders in initial stages. The current narrative review was planned to highlight auditory brainstem response recording's basic principles, uses and methods of interpretation in health and disease phases.

Keywords: Auditory brainstem response, Electrocochleogram, Auditory pathway, Retrocochlear pathologies, Meniere's disease.

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Introduction

Evoked potentials (EPs) are electrical potentials that occur in a group of neurons in response to stimulation of a sensory organ which can be recorded by surface electrodes. EP testing is useful for assessing the integrity of neuronal pathways both at sensory and motor levels of neural control. They can objectively estimate the brain electrical response to the specific signals sent by sensory and motor nerve pathways. Evoked response testing help in the diagnosis of nervous system abnormalities, including hearing impairment, and can accurately infer in the assessment of different neurological functions.[1,2] Auditory brainstem response (ABR) testing is a useful clinical and strong tool to make clinical judgements about the presence of hearing impairment, with degree and type of hearing impairment in subjects where behavioural problems make hearing thresholds estimations very difficult and unreliable. The test in itself is an objective measure, but proper interpretation of the records is subjective. ABR measurement can accurately tell us about hearing threshold in patients with cognitive impairment who cannot follow instructions behaviourally.

ABR audiometry is a neurophysiological test to assess auditory pathway function in response to auditory (click) stimuli that generate impulses by the auditory neural pathway which can be recorded on the scalp by surface electrodes. Although it is not a direct measure of hearing, it gives an objective assessment of auditory pathway. It can detect the integrity of the auditory pathway as early as 25 weeks of gestation. ABRs are not affected by sleep, sedation or attention. ABR's main purpose in electrophysiological testing is to determine signal detection threshold and make an inference concerning functional integrity of the auditory pathway and its neural components.[3] Click-evoked ABRs are powerful and valuable neurophysiological markers and indicators to test auditory system function and development. For a long time, it was thought that the human auditory pathway in the brainstem reaches full maturity at the age of 2 years in humans, but recent research has indicated that the developmental trajectory may be prolonged until 5 years.[3,4] The current narrative review was planned to create awareness among medical professionals about the usefulness of this important neurophysiological test, and to explain important international guidelines about its procedures and interpretation.

Classification of Auditory Evoked Potentials (AEPs)

The specific neural activity lasting approximately half-a-second in the form of voltage fluctuations generated in response to the auditory pathway stimulation is called

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AEP. Hundreds of response repetitions after sound click stimuli are averaged and filtered to give us AEPs to emerge from the background spontaneous neuronal pool signals. There are additional non-neural interferences, such as electromyography activity and external electromagnetic generators, that need to be filtered. These signals are visualised on computer screens as time-voltage waveform complexes. Proper type and placement of the recording electrodes, amplifiers, specific filters and post-stimulus timeframe make it possible to detect neuronal pools activity arising from structures spreading out from cochlea up to the cerebral cortex.[5]

One of the most applied classifications for AEP is related to the latency period in which they appear in the waveform. They are commonly divided into three classes according to latency timeframes and are labelled as early onset, middle and long latency evoked response signals. Early AEPs are recorded up to 10 milliseconds (ms), middle latency evoked potentials (MLEP) are composed of complex waveforms that are recorded for 10-50ms after stimulus onset, while late latency, also known as cortical response, has a range from 80 to 800ms.[6]

Early Auditory Evoked Potentials

Early AEP waves are recorded up to 10ms after the stimulus. These waves depend upon the simultaneous synchronous firing of thousands of neurons in the ascending auditory pathway's initial synaptic relay stations. These include cochlear and brainstem AEPs, commonly known as the electrocochleogram (ECoG) and brainstem AEPs (BAEPs). These EPs are widely used in the assessment of clinical state of cochlea, auditory nerve and middle portion of the brainstem. Furthermore, these are used for the assessment of hearing, popularly in the screening of neonates and infants who are at risk of hearing impairment.[7,8]

Auditory Middle-Latency Response

The waveforms recorded following the early ABR up to 80ms are called the auditory middle-latency response (AMLR) which does not reach its mature morphology until adolescence, and is altered by sleep in children. The AMLR can be a valuable diagnostic tool for central auditory function, especially in combination with an ABR, because it provides information about the integrity of important auditory structures, such as the brainstem, thalamus, thalamo-cortical pathway and primary auditory cortices. Performing a combined ABR-AMLR test increases the sensitivity to detect the lesions along the central auditory pathway.[9]

Late-latency Auditory Responses

Late-latency responses (LLRs) are cortical in origin and are produced beyond 80ms and may last for more than 600ms depending on the cortical response evoked. They were the first to be discovered. LLRs are highly dependent upon stimulus type, recording location, recording technique, patient age and state. The LLRs may differ dramatically in morphology and timing and may overlap one another. They are of two major types; exogenous and endogenous responses. Like ABR and AMLR, exogenous responses are obligatory responses to a sound, while endogenous responses are recorded after specific stimuli or tasks performed. Both AMLR and LLR are named by beginning with letters P and N indicating positive or negative polarity, unlike ABR waveforms.[9] Further discussion of AMLR and LLR is out of the scope of the current review.

Preparation and Electrode Positions

According to international guidelines, a proper setup and following standardised procedure are essential for successful ABR assessment. All patients need proper preparations. There are essential instructions to be given to patients before coming for the test, like washing the hair with shampoo, avoiding any gel or oil applications, and, being very young, they need to come in a sleep-deprived state to avoid sedation. Moreover, preparations during the test performance are also essential for a successful recording. Important points to be addressed before starting the test relate to the kind of patient being tested, like infant, child, cognitive dysfunction, old age, etc., and the reason for referral. Also, before starting the test, one has to make sure that one has tested the whole setup, including both the supplies, like electrodes, gel etc., and equipment, like software, grounding, artefacts etc.[10]

Patient Instructions

The patient needs to be given very clear instructions preferably in the native language if the test needs to be performed without sedation. The test is a routine for the physician in the neurophysiology lab, but for the patient it is a new and sometimes frustrating environment. Try to make the patient and attendants relax, and explain the procedure to them. This will reduce their anxiety since they are coming with a variety of problems.

Usually parents are more anxious about general anaesthesia and its consequences. They need to be explained and reassured that chloral hydrate is a safe and short-acting anaesthetic. It is mandatory to be administered usually between 3 months and 6 years of age. Alternatively, diazepam can be administered in tense adult subjects. One should always encourage young children and young people to sleep naturally during the

procedure. This is why it is better to come in a sleep-deprived state. Also, sleep is facilitated by making the environment dark, quiet and comfortable.

Always explain to patients, or their parents, that the test is non-invasive, not painful and is a routine clinical procedure without any side-effects in non-sedated states. It is used for all ages, even for newborns, and does not have any risks for the patients. The test can be stopped at any time upon patient or parent's request.

Problems in ABR Measurements

Problems encountered during ABR measurements include two main types. Firstly, there are operator-related errors, like obtaining a sub-optimal, inadequate AEP record due to technical errors contaminating the main results, like incorrect equipment setting or poor electrode application. Secondly, there are subject-related errors if the patient is being non-cooperative or moving excessively during the test. Thirdly, noise and disturbance might make the environment frustrating and sometimes their solutions are more challenging as these interfere with AEP measurements. Usually, EEG and EP labs are confined to those parts of hospital where there is minimum people traffic and the area is isolated for sound and electrical appliances.

Recording Protocols

EP Recording Procedure

ECoGs and BAEPs are typically evoked by brief 'click' stimuli produced by activating an acoustic 19-transducer device by administering short duration of standardised square wave pattern of electrical pulses in monophasic fashion (e.g., 100ms). The resulting stimulus is a series of sound waves lasting several milliseconds. Stimulus settings and recording protocols for ABR are widely available (Table-1). The arrangement of montages for AEP

Table-1: Stimulus settings and recording protocols for ABR.

Parameters	Values
Stimulus Rate	9-11/sec
Stimulus Intensity	20-120 decibels (dB)
Pulse Duration	100 µsec
Stimulus character	Contralateral white noise (masking at 60 dB)
Number of recorded trials	2,000-4,000
Recommended montages	
Channel 1	Cz versus Ai
Channel 2	Cz versus Ac
LFF	10 Hz to 30 Hz
HFF	2,500 Hz to 3,000 Hz
Analysis time	15-20 msec

ABR: Auditory brain-stem response; Ai; Iipsilateral ear); Ac: Contralateral ear, Cz: Vertex, LFF: Low frequency filter, HFF: High frequency filter.

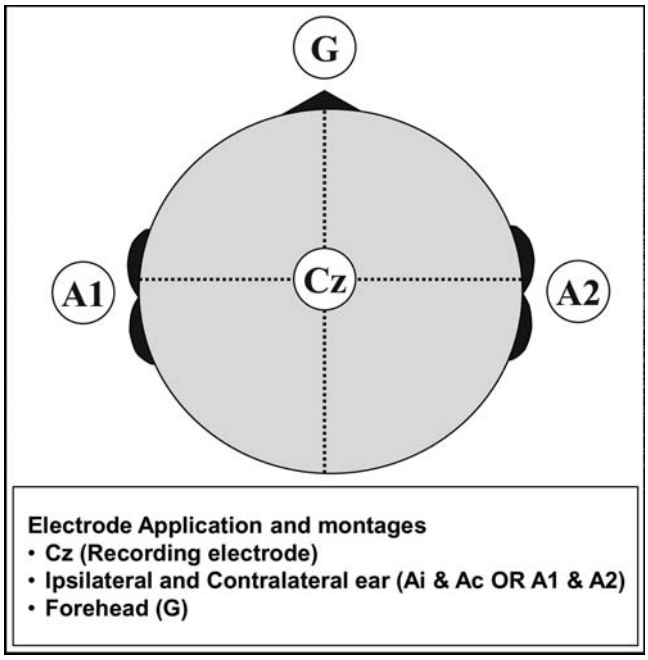

Figure-1: Electrode application and montages brain-stem auditory evoked potentials (BAEPs).

includes three important positions. Reference electrodes are placed on ipsilateral mastoid, which is labelled as A1 and A2 for left and right sides respectively, an active electrode at midline vertex (Cz) or/and ground (G) on the lower forehead (Figure-1). Silver surface electrodes are used for reference and ground electrodes. Alternating clicks of 100µsec duration are used. The appropriate adjustment for click stimulation is adjusted at frequency rate of 10 per second. The filter setting is adjusted between 10 and 200Hz. Record analysis time, which is commonly mentioned as sweep length, is adjusted at 100ms and gain sensitivity is adjusted to 0.2 micro-volt per division on screen. The adjustment of sound stimuli intensity is chosen according to the auditory threshold requirements or as desired. For example, the ipsilateral ear is stimulated with a desired intensity click ranging from 20 to 100 decibel (dB). The contralateral ear is given masking sound with white noise. About 1000 signals are averaged, recorded at least twice and overlapped for reproducibility in each ear separately.[11,12]

Interpretations

Waveform Generation and Identification

The waves routinely used in ABR analysis testing are expressed in roman numbers I, II, III, IV and V. Furthermore, waves VI and VII are also produced as part of short-latency responses, but usually they are not used in routine practice for interpretation in ABR measurements. It is always easier and recommended to identify waves IV

and V before other waves since they are produced as a part of two-peak complex, called IV V Complex. The generator of wave I is known to be from the most distal part of the acoustic nerve and its latency is approximately 2ms after giving the click stimuli. Wave I can be easily identified by simultaneously looking at the record from contralateral ear electrode. It is the only waveform that is formed only ipsilaterally and is not seen on the contralateral-side recording.[13]

The generator for wave V is thought to be from pontine projections to higher levels in the midbrain. Although some controversy still exists about the site of wave V generation, the popular belief is that it comes from inferior colliculus with an additional contribution from second-order neurons. The complexity of inferior colliculus is explained by the fact that the axons passing in the lateral lemniscus to inferior colliculus from lower brainstem regions relay in inferior colliculus by about 99%.[14] For waves VI and VII the actual generator site is still uncertain, but is thought to originate from higher centres in thalamic (medial geniculate body) regions. Many criteria are used to identify wave V. Its latency is about 6ms after stimulus onset and is often produced as wave IV-V combination to form IV-V joined complex waveform (Figure-2). This is the first waveform in ABR recordings in which falling slope sinks below the baseline.

On the contralateral side, wave IV has somewhat shorter latency and wave V is slightly longer because the wave III-V complex interpeak latency has a broader separation than the recording obtained from the ipsilateral ear. Wave V is the most robust of all wave forms and will appear up to the lowest intensities of 20dB. It is considered the last wave to disappear at lower intensities. Wave III is generated from the projections of superior olivary complex coming through the brainstem in lateral lemniscus. It appears as a prominent major peak between waves I and V.[10,11]

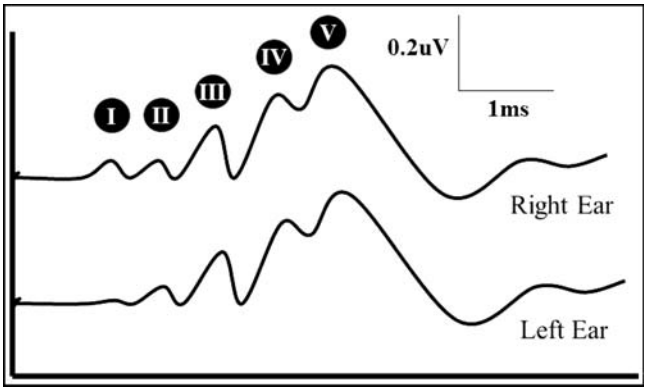

Figure-2: Normal auditory brain-stem response (ABR) recorded at 80 decibels (dB). The appearance can differ slightly, but the waves of interest are all convex up and have the almost similar appearance. Normal ABR in response to stimulation of the right ear (top) and masking in the left ear (bottom). [Note the absence of wave I in the contralateral recording]

ECoG waveforms tell us about the condition of cochlea. They are most probably originating from four cellular complexes, which are the inner hair cells, outer hair cells, the dendritic process potentials, and the spikes of auditory nerve fibres. In ECoG, two important waveforms are generated called summation potential (SP) and action potential (AP). SP is generated from the hair cells as they move in conjunction with the basilar membrane movements and is the stimulus generated potential in relation with cochlea. AP is believed to be the combined response from many auditory nerve fibres, usually in the thousands, that fire synchronously. For this reason, sometimes it is known as compound action potential.[15]

Waveform Analysis and Interpretation

There are two important aspects of waveform analysis; latency and amplitude. Waveforms analysis shows that latencies are more important interpretation than just the amplitude in EPs. Identification of waveforms is important and is sometimes misleading which may delude an inexperienced neurophysiologist. An easy way is to identify the waveforms from wave V backwards because it is the most robust and easily identifiable wave occurring at about 6ms with a steep rise and slow longer fall. The most important latency measurements are absolute and interpeak latencies with normative data from laboratory (Table-2). It is important to note that when the strength of sound clicks is decreased, waveforms start to decrease in amplitude and disappear. Only wave V can be detected up to 20dB. This determines the hearing threshold. Another important

Table-2: Reference range values of normal absolute and interpeak latencies in milliseconds and voltage in microvolts recorded at 80 decibels (dB).

Waveforms Analysis	Latencies Mean milliseconds	Normal Latencies SD	Amplitude (voltage in µv)
wave I latency	1.7	0.15	0.28
wave II latency	2.8	0.17	0.23
wave III latency	3.9	0.19	0.25
wave IV latency	5.1	0.24	0.40
wave V latency	5.7	0.25	0.47
I - III	2.2	0.15	
III - V	2.0	0.18	
I - V	4.2	0.23	
SP	<2.0		0.30
AP	<2.0		1.00
SP/AP			30%

SD: Standard deviation, SP: Summation potential, AP: Action potential, SP/AP: Summation and Action potential ratio.

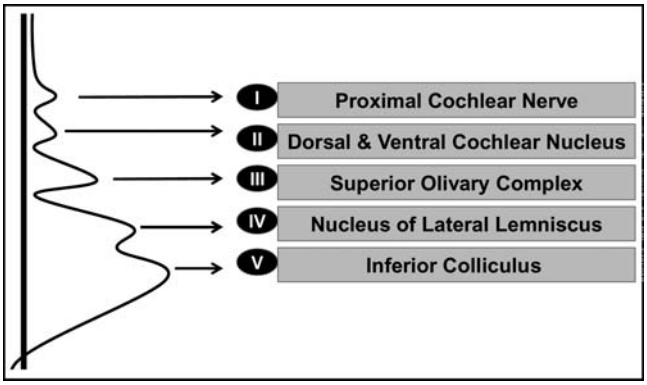

Figure-3: Waveform generators in auditory pathway.

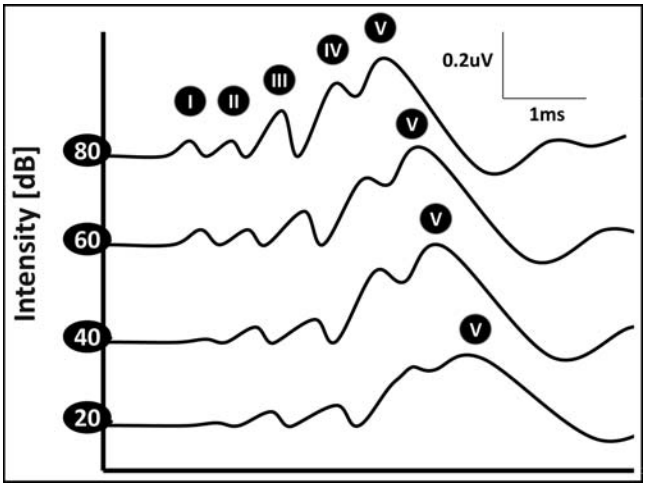

Figure-4: Normal auditory brain-stem response (ABR) waves recorded at 80, 60, 40 and 20 decibels (dB). The appearance differs between various sound intensities. All waves get delayed with decrease in amplitude and ultimately disappear with decreasing sound intensity. Only wave V remains up to 20dB.

analysis is detection of threshold for wave V. It is determined by the lowest click's strength for wave V appearance, which in normal persons is up to 20dB. It should be noted that the appearance of waveforms

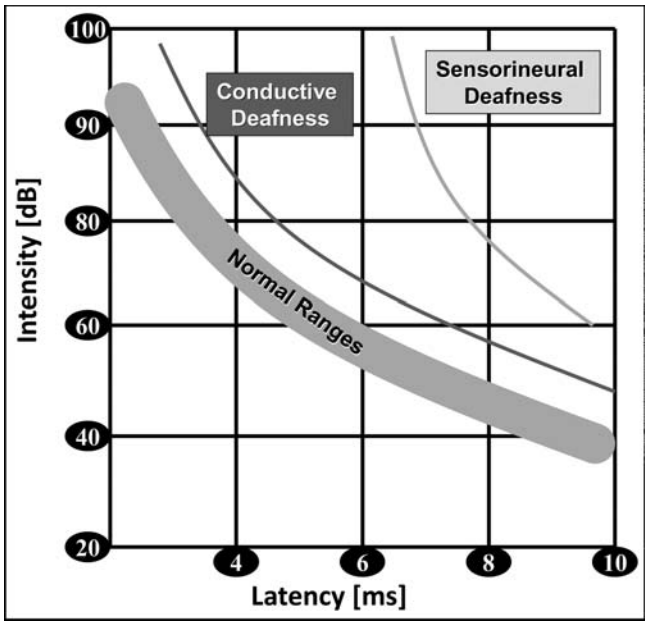

Figure-5: Latency intensity curve plotted at different sound intensities with normal ranges, sensorineural deafness and conductive deafness patterns.

differs between various sound intensities. As the stimulus intensity is decreased, waveform latencies increase proportionally in a systematic manner up to lower hearing thresholds, below which no reproducible response is reached or recorded. All waves get delayed symmetrically with decrease in amplitude and ultimately disappear with decreasing sound intensity. Only wave V remains up to 20dB (Figure-3). Figure-4 shows a normal auditory brain stem response at different decibel levels (Figure-4). An additional useful measure is the latency intensity curve estimation.[16-18] It is constructed by plotting the latencies of wave V at different levels of sound intensities (Figure-5).

In sensorineural hearing loss (SNHL), the curve shows high thresholds and the lines are not parallel to the

Table-3: Interpretation of abnormalities in different BAEP findings.

Waveforms Findings	Interpretation
Increased wave I latency	Lesion most probably in distal part of acoustic nerve.
Increased I-III interpeak interval	Lesion in auditory pathway from proximal VIII N into contralateral lower pons that is seen in cerebellopontine angle tumours like Acoustic Neuroma, subarachnoid space inflammations or Pontomedullary Junction lesions
Increased III-V interpeak interval	Lesions is situated between Lower pons to upper pons or lower midbrain eg in demyelination or tumours of these regions
Increased I-III and III-V interpeak intervals	Lesions of brainstem above caudal pons or caudal pons and acoustic nerve. Slow conduction from VIII nerve to midbrain (eg;demyelination, ischaemia, tumours and other degenerative diseases)
Absence of wave I with normal III and V	Peripheral hearing disorders. Conduction in the caudal pons cannot be evaluated.
Absence of wave III with normal I and VI	Normal study
Absence of wave V with normal I and III	Lesion above the caudal pons, considered an extreme of wave III-V interpeak interval prolongation.
Absence of all waves	Profound hearing loss.

BAEP: Brain-stem auditory evoked potentials.

normal curve, while in conductive hearing loss the lines are parallel to the normal curve. Abnormalities of different lesions encountered should also be kept in mind (Table-3).

Important Clinical Conditions and Brainstem Audiometry

AEPs have been used in many important clinical conditions, ranging from rare to commonly-encountered conditions. Although the details of these conditions and EP findings are out of the scope of the current review, a brief overview of some problems is essential. In Mennier's disease there is fluctuating unilateral SNHL, tinnitus and episodic vertigo. Progressive deafness occurs over years. Mennier's disease AP is smaller than SP and is reversed, and SP/AP $\geq$0.45 is considered abnormal. The iatrogenic complications rate has been reduced to almost none with intraoperative monitoring.[19] The use of EPs in surgeries is mostly related to cerebellopontine angle tumours e.g., acoustic neuroma. Furthermore, these tests provide useful diagnostic information in patients with idiopathic sudden SNHL (ISSNHL) in addition to pure tone audiometry. Patients with ISSNHL have significant abnormalities in BAEP and ECoG recordings showing predominantly cochlear involvement.[20] The usefulness of ABR has been reported in sickle cell disease complications.[21] Less popular uses are in resistant migraine headache (increased latencies) and brainstem stroke. Moreover, disappearance of wave V is a clear sign of brain death.[22-24]

Future Prospects and Recommendations

With advancements in recent technologies, ABR testing is set to explore further the condition of auditory nerve and brainstem pathways involved in hearing in both qualitative and quantitative aspects. An integrated approach in the future is aimed at encompassing functional magnetic resonance imaging (fMRI), evoked responses, non-invasive brain stimulation and standardised neurocognitive assessment tools. However, universal standardised guidelines are needed for proper ABR testing and its interpretations. Moreover, evidence-based studies are required on standardising the procedures to obtain valid EP recordings that may accurately diagnose auditory pathway disorders and give an accurate measure of hearing thresholds.

Conclusions

ABR audiometry has many clinical applications, including routine newborn hearing screening and detecting retrocochlear pathologies. Additionally, it is useful during neurosurgical procedures in intraoperative monitoring, estimating frequency-specific auditory sensitivity, monitoring cases in intensive care units, and diagnosing suspected demyelinating diseases, like multiple sclerosis.

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