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NEUROPHYSIOLOGICAL CORRELATES OF DEPRESSION SEVERITY IN MAJOR DEPRESSIVE DISORDER USING BRAINSTEM AUDITORY EVOKED POTENTIALS

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ABSTRACT

Background: Major Depressive Disorder (MDD) is associated with neurophysiological abnormalities involving brainstem auditory pathways. Brainstem Auditory Evoked Potentials (BAEPs) provide an objective assessment of auditory pathway conduction and brainstem function. The aim is to evaluate the neurophysiological correlates of depression severity in patients with Major Depressive Disorder using BAEP.

Materials and Methods: This cross-sectional observational study included patients diagnosed with MDD. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D), and participants were categorised into mild, moderate, and severe groups. BAEP recordings were obtained under standard laboratory conditions. Absolute latencies of Waves I, III, and V and interpeak latencies (I–III, III–V, and I–V) were analysed bilaterally. Statistical analysis was performed using one-way ANOVA.

Results: Among the 133 drug-naïve patients with Major Depressive Disorder, BAEP analysis demonstrated a significant association between depression severity and selected auditory brainstem conduction parameters. Absolute Wave V latency and Interpeak Wave I–V latency were significantly prolonged with increasing HAM-D severity in both the right ($p = 0.037$ and $p = 0.036$, respectively) and left ears ($p = 0.039$ and $p = 0.038$, respectively). No statistically significant differences were observed in Absolute Wave I, Absolute Wave III, Interpeak Wave I–III, or Interpeak Wave III–V latencies across the severity groups.

Conclusion: Increasing severity of Major Depressive Disorder is associated with significant prolongation of Absolute Wave V and Interpeak Wave I–V latencies in both ears, while early BAEP components remain unaffected. These findings suggest selective impairment of central auditory brainstem conduction with increasing depression severity and indicate that Wave V and Interpeak Wave I–V latencies may serve as objective neurophysiological biomarkers for assessing disease severity in Major Depressive Disorder.

Keywords: Major Depressive Disorder (MDD); Brainstem Auditory Evoked Potential (BAEP); Depression Severity; Hamilton Depression Rating Scale (HAM-D); Auditory Brainstem Response (ABR).

INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent psychiatric illness characterised by persistent low mood, anhedonia, cognitive impairment, psychomotor disturbances, sleep abnormalities, and reduced functional capacity. It is one of the leading causes of disability worldwide and contributes

substantially to the global burden of disease.[1] Despite significant advances in psychiatric research, the neurobiological mechanisms underlying MDD remain incompletely understood. Contemporary evidence suggests that depression involves complex interactions among neurotransmitter dysregulation, neuroendocrine abnormalities, inflammatory pathways, circadian rhythm disturbances, and altered neural connectivity within cortical and subcortical brain regions.[2,3]

Recent neurophysiological research has increasingly focused on identifying objective biomarkers that may improve the understanding, diagnosis, and assessment of depressive disorders. Among various electrophysiological techniques, Brainstem Auditory Evoked Potentials (BAEP), also referred to as Auditory Brainstem Responses (ABR), provide a non-invasive and reproducible method for evaluating the integrity and conduction velocity of auditory pathways within the brainstem.[4] BAEP recordings consist of a sequence of waves generated by synchronous neural activity from the auditory nerve to the midbrain following auditory stimulation. Alterations in wave latencies and interpeak conduction times may reflect dysfunction of brainstem neuronal transmission and impaired neural synchronisation.[5]

The brainstem contains several monoaminergic nuclei, including the raphe nuclei and locus coeruleus, which are critically involved in mood regulation, arousal, emotional processing, and neurotransmitter modulation.[6] Dysfunction of serotonergic and noradrenergic systems originating from these nuclei has been strongly implicated in the pathophysiology of depression.[7] Since BAEP responses are generated within these neuroanatomical regions, abnormalities in auditory brainstem conduction may represent objective indicators of subcortical dysfunction associated with depressive illness.

Several investigators have reported prolonged absolute wave latencies and interpeak latencies in patients with psychiatric disorders, including Major Depressive Disorder, suggesting delayed neural conduction and impaired information processing within auditory pathways.[8,9] Electrophysiological abnormalities observed in depression may result from altered neurotransmitter activity, impaired synaptic transmission, reduced neuronal plasticity, or functional disturbances within brainstem circuits.[10] However, findings across studies remain inconsistent, and limited data are available regarding the relationship between BAEP abnormalities and the severity of depressive symptoms.

The Hamilton Depression Rating Scale (HAM-D) is one of the most widely used clinician-administered instruments for evaluating the severity of depression.[11] Correlating BAEP parameters with HAM-D severity scores may help establish objective neurophysiological markers that reflect clinical severity and disease progression in MDD. Such biomarkers may contribute to improved diagnostic precision and development of personalised treatment strategies.

In the present study, we evaluated Brainstem Auditory Evoked Potential parameters in patients with Major Depressive Disorder and compared them across varying levels of depression severity assessed using HAM-D scores. The study aimed to investigate whether increasing severity of depressive symptoms is associated with progressive alterations in auditory brainstem conduction, thereby providing insight into the neurophysiological correlates of depression severity.

MATERIALS AND METHODS

The present study was designed as a cross-sectional observational study was conducted in the Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences (RMLIMS), Lucknow (Uttar Pradesh) India, in collaboration with the Department of Psychiatry at same institute. The study was carried out over a defined study period after obtaining approval from the Institute Ethics Committee (REF. NO. 1091/RMLIMS/2024; IEC NO. 80/24). All participants were informed in detail about the objectives and procedures of the study, and written informed consent was obtained prior to enrolment. The study protocol was in accordance with the ethical principles outlined in the Declaration of Helsinki, and participant anonymity and data confidentiality was maintained throughout the study.

A total of 133 patients diagnosed with Major Depressive Disorder (MDD) were recruited consecutively from the outpatient and inpatient services of the Department of Psychiatry Dr. RMLIMS Lucknow (U.P.) India. The diagnosis of MDD was established by a qualified psychiatrist using on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Participants of both genders, aged between 18 and 45 years, diagnosed with MDD and without clinically evident hearing impairment were included in the study. Patients with a history of neurological disorders, otological diseases, hearing loss, substance abuse or dependence, comorbid psychiatric disorders, systemic illnesses known to affect auditory pathways, or those receiving medications known to influence auditory evoked potentials were excluded from the study.

Severity of major depressive disorder assessed by Hamilton Depression Rating Scale (HAM-D). Although it contains 21 items, calculate the patients score on the first 17. If, score 0-7 normal, 8-13 mild depression, 14-18 moderate depression, 19-22 severe depression, ≥23 very severe depression.

Brainstem Auditory Evoked Potentials (BAEPs) were recorded in all participants using using Neuro-MEP.NET (Neurosoftware version 4.4.9.0), a standard computerized evoked potential recording system in a sound-attenuated and electrically shielded room. Participants were instructed to abstain from caffeine and nicotine for at least 12 hours before

testing and were allowed adequate rest prior to the procedure. Recordings were performed with the participants in a relaxed supine position with eyes closed to minimize movement and muscle artifacts. After appropriate skin preparation, silver–silver chloride disc electrodes were placed according to the International 10–20 system, with the reference electrode at the vertex (Cz), active electrodes on the ipsilateral and contralateral mastoids, and the ground electrode on the forehead. Inter-electrode impedance was maintained below 5 kΩ throughout the recording. Auditory stimulation consisted of rarefaction clicks of 100 µs duration delivered monaurally through insert earphones at an intensity of 70 dB above the individual hearing threshold. The stimulus repetition rate was set at 11.1 clicks per second, and masking noise was applied to the non-test ear. The evoked responses were amplified, band-pass filtered between 100 and 3000 Hz, and averaged over 2000 stimulus presentations to obtain clear and reproducible waveforms. Each recording was repeated to ensure waveform consistency and reliability.

The absolute latencies of BAEP waves I, III, and V and the inter-peak latencies I–III, III–V, and I–V were measured for both ears, and mean values were considered for analysis.

Statistical analysis was performed using MS Excel and R-4.2.3 statistical software. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequency and proportion. The normality of data distribution was assessed using the Shapiro–Wilk test. Since the BAEP latency parameters were normally distributed, comparisons of mean BAEP latencies among the three Hamilton Depression Rating Scale (HAM-D) severity groups (mild, moderate, and severe) were performed using one-way Analysis of Variance (ANOVA). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 133 patients with Major Depressive Disorder (MDD) were evaluated for depression severity using the Hamilton Depression Rating Scale (HAM-D) and assessed for Brainstem Auditory Evoked Potential (BAEP) parameters. Participants were categorised into mild, moderate, and severe depression groups according to HAM-D scores.

Comparative analysis of absolute and interpeak latencies among the different severity groups was performed using one-way analysis of variance (ANOVA), as shown in [Table 1 and Figure 1].

In the right ear, the mean Absolute Wave I latency showed a slight increase from 1.52 ± 0.05 ms in patients with mild depression to 1.54 ± 0.05 ms in those with severe depression; however, this difference was not statistically significant ($p = 0.329$). Similarly, Absolute Wave III latency increased marginally from 4.02 ± 0.08 ms to 4.05 ± 0.08 ms, but the difference was not statistically significant ($p = 0.238$).

A statistically significant increase was observed in Absolute Wave V latency, which increased from 5.85 ± 0.32 ms in the mild depression group to 5.96 ± 0.35 ms in the moderate group and 6.04 ± 0.38 ms in the severe group ($p = 0.037$). Among the interpeak latencies, Wave I–III and Wave III–V did not show statistically significant differences across the three severity groups ($p = 0.281$ and $p = 0.252$, respectively). In contrast, Interpeak Wave I–V latency demonstrated a significant increase with increasing depression severity, rising from 4.64 ± 0.28 ms in mild depression to 4.86 ± 0.34 ms in severe depression ($p = 0.036$).

Similarly, in the left ear, Absolute Wave I and Absolute Wave III latencies did not differ significantly among the HAM-D severity groups ($p = 0.342$ and $p = 0.259$, respectively). However, Absolute Wave V latency increased significantly from 5.84 ± 0.31 ms in patients with mild depression to 6.03 ± 0.36 ms in those with severe depression ($p = 0.039$).

No statistically significant differences were observed in Interpeak Wave I–III ($p = 0.291$) and Interpeak Wave III–V ($p = 0.272$) latencies. In contrast, Interpeak Wave I–V latency showed a significant increase from 4.63 ± 0.27 ms in mild depression to 4.85 ± 0.33 ms in severe depression ($p = 0.038$).

Overall, the findings indicate that Absolute Wave V latency and Interpeak Wave I–V latency were significantly prolonged with increasing severity of depression in both ears, whereas Absolute Wave I, Absolute Wave III, Interpeak Wave I–III, and Interpeak Wave III–V latencies did not show statistically significant differences among the HAM-D severity groups. These results suggest impaired auditory brainstem conduction and altered neurophysiological processing in individuals with higher HAM-D scores, supporting the role of BAEP as a potential objective biomarker for severity assessment in Major Depressive Disorder.

Table 1: Comparison of Brainstem Auditory Evoked Potential (BAEP) parameters among patients with mild, moderate and severe Major Depressive Disorder based on Hamilton Depression Rating Scale (HAM-D) scores.

Sr. No.	Variable	BAEP Parameter	Hamilton Depression Rating Scale (HAM-D)			p-value
			Mild Mean ± SD (N=43)	Moderate Mean ± SD (N=26)	Severe Mean ± SD (N=64)	
1.	Right Ear	ABSOLUTE WAVE(I)	1.52 ± 0.05	1.53 ± 0.04	1.54 ± 0.05	0.329
		ABSOLUTE WAVE(III)	4.02 ± 0.08	4.04 ± 0.07	4.05 ± 0.08	0.238
		ABSOLUTE WAVE(V)	5.85 ± 0.32	5.96 ± 0.35	6.04 ± 0.38	0.037*
		INTERPEAK WAVE(I-III)	2.61 ± 0.07	2.63 ± 0.08	2.64 ± 0.07	0.281
		INTERPEAK WAVE(III-V)	2.63 ± 0.06	2.65 ± 0.07	2.66 ± 0.06	0.252
		INTERPEAK WAVE(I-V)	4.64 ± 0.28	4.78 ± 0.31	4.86 ± 0.34	0.036*

2.	Left Ear	ABSOLUTE WAVE(I)	1.52 ± 0.05	1.53 ± 0.05	1.54 ± 0.05	0.342
		ABSOLUTE WAVE(III)	4.01 ± 0.08	4.03 ± 0.07	4.04 ± 0.08	0.259
		ABSOLUTE WAVE(V)	5.84 ± 0.31	5.95 ± 0.34	6.03 ± 0.36	0.039*
		INTERPEAK WAVE(I-III)	2.60 ± 0.07	2.62 ± 0.07	2.63 ± 0.08	0.291
		INTERPEAK WAVE(III-V)	2.63 ± 0.06	2.64 ± 0.07	2.65 ± 0.06	0.272
		INTERPEAK WAVE(I-V)	4.63 ± 0.27	4.77 ± 0.30	4.85 ± 0.33	0.038*

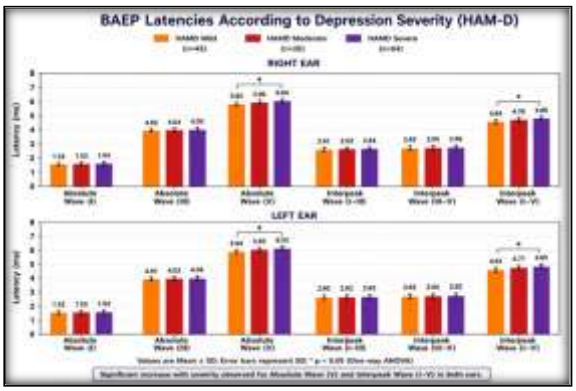

Figure 1: illustrates the comparison of Brainstem Auditory Evoked Potential (BAEP) latencies among patients with mild, moderate, and severe Major Depressive Disorder according to Hamilton Depression Rating Scale (HAM-D) scores.

DISCUSSION

The present study demonstrated that Absolute Wave V latency and Interpeak Wave I–V latency were significantly prolonged in both ears with increasing severity of depression, whereas Absolute Wave I, Absolute Wave III, Interpeak Wave I–III, and Interpeak Wave III–V latencies did not differ significantly among the HAM-D severity groups. These findings suggest that depression severity is associated with delayed neural conduction in the higher auditory brainstem pathways, particularly at the level of the lateral lemniscus and inferior colliculus, while conduction through the peripheral auditory nerve and lower brainstem structures remains relatively preserved.[13-16]

The findings of the present study are partially consistent with those reported by Gupta et al,[12] who compared BAEP parameters among patients with mild, moderate, and severe depression. They observed statistically significant differences in Right Ear Wave I latency and Left Ear Interpeak Wave I–III latency among the three severity groups, suggesting that electrophysiological abnormalities increase with worsening depressive symptoms. Although the present study identified significant prolongation of Wave V and Interpeak Wave I–V latency rather than the earlier BAEP components, both studies support the concept that increasing depression severity is associated with measurable dysfunction of the auditory brainstem. The variation in the affected BAEP parameters may be explained by differences in sample size, demographic characteristics, disease duration, severity distribution, recording techniques, and statistical methodology.

The selective prolongation of Wave V latency observed in the present study is physiologically important. Hall et al,[13] described Wave V as the most robust and clinically reliable component of the BAEP because it is generated predominantly by the lateral lemniscus and inferior colliculus. Owing to its stability and reproducibility, Wave V is considered the most sensitive BAEP component for detecting abnormalities in central auditory conduction. Therefore, prolongation of Wave V in patients with severe depression may indicate impaired neuronal synchronisation within higher brainstem auditory pathways.

Similarly, Chiappa et al,[14] reported that prolongation of Wave V and Interpeak Wave I–V latency is one of the most sensitive electrophysiological indicators of brainstem dysfunction. They emphasized that increased Wave I–V conduction time reflects delayed transmission of neural impulses from the auditory nerve to the midbrain rather than abnormalities of cochlear function. This explanation closely supports the findings of the present study.

The observations of the present study are also supported by Picton et al,[15] who demonstrated that BAEP provides an objective measure of neural synchrony within the auditory pathways. According to Picton and colleagues, delayed Wave V latency reflects impaired synchronisation of neuronal firing in the ascending auditory brainstem. Since Major Depressive Disorder is associated with abnormalities in monoaminergic neurotransmission and impaired neuronal connectivity, delayed Wave V latency may represent reduced efficiency of neural transmission within central auditory pathways.

Furthermore, Møller et al,[16] explained that BAEP abnormalities primarily reflect dysfunction of brainstem neuronal networks rather than peripheral hearing impairment. They proposed that delayed Wave V and prolonged Interpeak Wave I–V latency indicate impaired conduction through the upper brainstem structures. The present findings are in agreement with these physiological observations, as early BAEP waves remained relatively unchanged while later brainstem components demonstrated significant prolongation.

The absence of statistically significant differences in Absolute Wave I and Absolute Wave III latencies in the present study suggests that depression severity does not substantially affect the auditory nerve or lower pontine auditory relay nuclei. Instead, the significant increase in Wave V and Interpeak Wave I–V latency indicates preferential involvement of higher brainstem structures. This finding supports the hypothesis that neurophysiological dysfunction in Major Depressive Disorder predominantly involves

central rather than peripheral auditory pathways.[13–16]

Several neurobiological mechanisms may account for these observations. Major Depressive Disorder is characterized by abnormalities in serotonergic, noradrenergic, and dopaminergic neurotransmission, dysregulation of Hypothalamic-Pitutary-Adrenal axis, neuroinflammation, oxidative stress, impaired synaptic plasticity, and reduced neuronal synchrony. These pathological changes can slow conduction through the auditory brainstem, resulting in prolonged BAEP latencies. Experimental and clinical evidence suggests that these neurochemical alterations become more pronounced with increasing depression severity, thereby contributing to delayed Wave V generation and prolonged overall brainstem conduction time.[13–16]

From a clinical perspective, the findings of the present study indicate that Absolute Wave V latency and Interpeak Wave I–V latency may serve as objective neurophysiological markers of depression severity. Because BAEP is a non-invasive, reproducible, and objective investigation that is independent of patient cooperation, these parameters may complement conventional clinical assessment using the Hamilton Depression Rating Scale. However, further multicentric longitudinal studies with larger sample sizes are required to establish the prognostic value of BAEP in Major Depressive Disorder.

CONCLUSION

The present study evaluated the association between Brainstem Auditory Evoked Potential (BAEP) parameters and the severity of Major Depressive Disorder (MDD) as assessed by the Hamilton Depression Rating Scale (HAM-D). The findings demonstrated that Absolute Wave V latency and Interpeak Wave I–V latency were significantly prolonged in both ears with increasing severity of depression, whereas Absolute Wave I, Absolute Wave III, Interpeak Wave I–III, and Interpeak Wave III–V latencies did not show statistically significant differences among the mild, moderate, and severe depression groups.

These findings indicate that increasing depression severity is associated with delayed neural conduction predominantly within the higher auditory brainstem pathways, particularly involving the lateral lemniscus and inferior colliculus, while peripheral auditory nerve function and lower brainstem conduction remain relatively preserved. The selective prolongation of Wave V and Interpeak Wave I–V latency suggests dysfunction of central auditory processing associated with the neurobiological changes occurring in Major Depressive Disorder.

The present study further supports the potential role of BAEP as an objective, non-invasive, and reproducible neurophysiological tool for evaluating brainstem dysfunction in patients with depression. Among the BAEP parameters studied, Absolute Wave V latency and Interpeak Wave I–V latency emerged as the most sensitive electrophysiological markers of depression severity.

In conclusion, the study demonstrates that Brainstem Auditory Evoked Potentials, particularly Wave V and Interpeak Wave I–V latency, may serve as valuable objective biomarkers for assessing the severity of Major Depressive Disorder. Incorporation of BAEP into clinical and research settings may complement conventional psychiatric assessment and improve the understanding of the neurophysiological basis of depression. However, further multicentric longitudinal studies with larger sample sizes are required to validate these findings and to determine the utility of BAEP in monitoring disease progression and response to antidepressant therapy.

Limitations

1. The study was conducted with a relatively small sample size, which may limit generalisability of the findings.
2. The cross-sectional design precludes assessment of causal relationships between BAEP abnormalities and depressive illness.
3. Medication status and duration of illness may have influenced electrophysiological parameters.
4. The study did not include neuroimaging or biochemical correlation, which could provide additional insight into underlying neurobiological mechanisms.
5. Longitudinal follow-up was not performed to evaluate changes in BAEP parameters after treatment or remission of depressive symptoms.

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