



Original Article

Speech–Evoked Auditory Brainstem Response in Individuals with Diabetes Mellitus Type 2

Himanshu Kumar Sanju, Akhil Mohanan, Prawin Kumar

All India Institute of Speech and Hearing, Mysuru-6, Karnataka, India

OBJECTIVE: Diabetes is the most common glucose level dependent metabolic disorder and studies have shown that hearing impairment can be a long-term subclinical complication. Studies to investigate auditory system involvement in diabetes has focused majorly on the auditory brainstem response (ABR), otoacoustic emission, and basic audiological measures. Hence in the current study, we used speech-evoked ABR (S-ABR) as a tool to see the effect of diabetes on both a transient and sustained response of the auditory brainstem to a conventionally used consonant-vowel (CV) stimuli /da/.

MATERIALS and METHODS: This preliminary investigation was done on 22 individuals in the age range of 40–55 years. 11 individuals were diabetics for a minimum period of five years. The S-ABR was recorded for all the participants with speech stimuli /da/ of 40 ms duration. Latency analysis of the waves V, A, D, E, F, and O were carried out. The statistical analysis included descriptive measures, paired t tests, and MANOVA.

RESULTS: The findings of the current study suggest that middle-aged individuals with diabetes have a significant deficiency in auditory processing at the brainstem level. Both transient (wave V ($p=0.00$), A ($p=0.00$), and O ($p=0.00$)) and sustained responses (wave D ($p=0.001$), E ($p=0.00$), and F ($p=0.00$)) of the S-ABR were found to be affected in diabetic individuals compared to age-matched non-diabetic individuals.

CONCLUSION: Considering diabetes is a common metabolic disorder in the middle-aged Indian population, the findings of the present study can have significant clinical implication.

KEYWORDS: Diabetes mellitus, type 2, speech, auditory brainstem response

INTRODUCTION

Diabetes mellitus refers to a group of metabolic disorders with marked elevation of blood sugar and altered insulin secretion and action^[1]. Ramachandran et al.^[2], 2010 has reported that 50.8 million people are suffering from diabetes in India, whereas it has been estimated to be reaching 87 million by 2030. The prevalence of diabetic adults in the southern states of India is about 20% and 10% in urban and rural populations, respectively^[3]. Approximately 90%–95% are diabetes mellitus type 2 or adult onset diabetes mellitus type 1. There are well established subclinical complications of diabetes, including retinopathy, nephropathy, and peripheral neuropathy.

The link between diabetes and hearing loss has also been investigated widely^[4–8]. The earliest discussion of diabetes and hearing impairment is credited to the work of Jordao in 1857^[8]. In spite of the wide literature that has been devoted to this topic, the relationship between diabetes and hearing impairment has not been clearly established yet. Although the majority of authors claim that diabetes causes hearing impairment, others suggest that there is no clear association between diabetes and hearing impairment^[9–11]. However, most of the previous studies explored the relationship between diabetes and hearing impairment using click-evoked auditory brainstem response only^[6,7]. In these studies, the inter-peak latencies I-III, III-V, and I-V have been significantly found to be delayed^[5,12–14]. Even though the click-evoked ABR is the gold standard for assessing neural encoding of acoustic stimuli at the brainstem level, it does not account for behaviorally relevant complex signal processing, such as speech^[15]. A speech stimulus is complex and it contains less high frequency information as compared to the click stimulus; hence, it needs different acoustic processing at the brainstem level. Investigating the brainstem representation of speech stimuli will give insight into some of the subcortical auditory processes involved in speech perception^[16,17].

Researchers have assessed the brainstem encoding of speech stimuli by utilizing S-ABR. The majority of the investigations recorded S-ABR using the synthetic /da/ syllable of 40 ms duration^[16]. The /da/ stimulus has been phenomenal in assessing both transient and periodic responses of neural encoding. Human brainstem structures are key components in encoding auditory temporal information. S-ABR is an important tool for evaluating the brainstem's ability to encode temporal information. Any

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delay in the temporal processing will reflect an abnormal results in S-ABR [17]. The outcomes using /da/ stimuli in various disorders show abnormal temporal characteristics at the brainstem level [18, 19]. As mentioned earlier, studies that investigated the auditory system involvement in diabetes mellitus focused mainly on either click-evoked ABR or basic audiological evaluations including pure-tone audiometry and otoacoustic emission [4, 5]. However, there is a dearth of literature regarding the speech processing abilities in these individuals. There are limited studies in the auditory processing abilities of glucose-level dependent metabolic disorders. McCrimmon et al. [20] assessed the auditory temporal processing in non-diabetic individuals with insulin-induced hypoglycemia. Their finding suggests that auditory temporal processing is significantly affected in non-diabetic individuals with hypoglycemia. Evoked potentials and nerve conduction studies have clearly shown the involvement of central and peripheral neuropathy in diabetes mellitus [21]. The hypothesis of the study was that disturbed brainstem encoding of speech occurred in individuals with diabetes mellitus type 2. Considering this, there is a need to investigate the outcome with S-ABR in individuals with diabetes mellitus type 2. The current study aimed at comparing the S-ABR responses of middle-aged diabetes mellitus type 2 individuals with age-matched non-diabetic individuals.

MATERIALS and METHODS

Participants

This study was approved by the ethical committee at the All India Institute of Speech and Hearing, Mysuru-6, Karnataka, India. A total of 22 right-handed participants aged 40-55 years (mean age: 48.27 years) participated in the study. Informed written consent was obtained from all participants. These subjects were divided into two groups. Group I included 11 age-matched individuals that were not diabetic as confirmed by a physician. Group II served as the experimental group and consisted of 11 individuals diagnosed with diabetes mellitus type 2 with a duration of at least 5 years. The diagnosis of diabetes mellitus was confirmed by a physician based on the blood glucose measurements including average blood sugar level over the previous three months (HbA1C testing), fasting plasma glucose test, and oral glucose tolerance test, as shown in Table 1. All the participants had bilateral normal hearing sensitivity as defined by audiometric thresholds (PTA ≤ 15 dBHL) and speech audiometry testing. Participants who had any history of neurological problems, ototoxicity, and chronic noise exposure were excluded from the study.

Instrumentation

A calibrated dual channel diagnostic audiometer GSI 61 (Grason-Stadler, Eden Prairie, Minnesota) with supra-aural headphones (TDH-39) were used for obtaining air-conduction thresholds, Speech Recognition Threshold (SRT), and Speech Identification Score (SIS). The same audiometer with a RadioEar B-71 bone-vibrator (RadioEar, New Eagle, PA) was used for obtaining bone-conduction thresholds. A calibrated acoustic immittance meter (GSI Tymstar) (Grason-Stadler, Eden Prairie, Minnesota) with a probe tone frequency of 226 Hz was used for tympanometry and stapes reflex testing. A Bio-logic Navigator Pro (Navigator Pro AEP, Pleasanton, CA) (version 7.0) with an Etymotic ER-3 insert earphones were used for recording click as well as S-ABR.

Procedure

Pure tone thresholds were obtained using a modified version of the Hughson and Westlake procedure to establish normal hearing sensitivity [22]. Air conduction thresholds were obtained for octave frequencies between 250 Hz and 8 kHz, whereas bone conduction thresholds were measured at octave frequencies between 250 Hz and 4 kHz. SRT and SIS were obtained using spondee words and monosyllabic phonetically balanced words, respectively. These tests were administered in the participants' native language using live monitored speech. To rule out any middle ear pathology, acoustic immittance and stapes reflex testing were carried out. An acoustic immittance meter test was performed using a 226 Hz probe tone. Stapes reflex testing was tested with ipsilateral and contralateral acoustic reflexes at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz with the same 226 Hz probe tone. A Bio-logic Navigator Pro (version 7) was used to record click-evoked ABR to check the integrity of the neural pathway at the brainstem level prior to measuring the S-ABR. The S-ABR was recorded from all the participants with speech stimuli /da/ of 40 ms duration produced using a KLATT synthesizer (Figure 1) [23]. Silver chloride disk electrodes were used to record the responses. Recording was done ipsilaterally with electrodes at the vertex (non-inverting), ipsilateral mastoid (inverting), and contralateral mastoid (ground). The absolute electrode impedance and inter-electrode impedance were maintained below 5 kΩ and 2 kΩ, respectively. At least two recordings of 3000 sweeps to rarefaction polarity at a rate of 10.9/s were collected. The responses were amplified 100,000 times and a weighted addition of the two recordings were taken for analysis. A time window of 64 ms, including 10 ms pre-stimulus time, was used. The responses were band pass filtered online between 100-2000 Hz. The stimuli were presented through Etymotic ER-3A insert earphones and the intensity level was set to 80 dB SPL (Table 2). The stimulus is presented from BIOLOGIC

Table 1. Average blood sugar level over the previous three months (HbA1C testing), fasting plasma glucose, and oral glucose tolerance test of all subjects

	HbA1C* (%)	Fasting plasma glucose (mg/dL)	Oral glucose tolerance (mg/dL)
Diabetes mellitus type-2	7.9	159.3	220.6
Non-diabetic	4.1	81.2	101.7

*HbA1C-Hemoglobin A1c

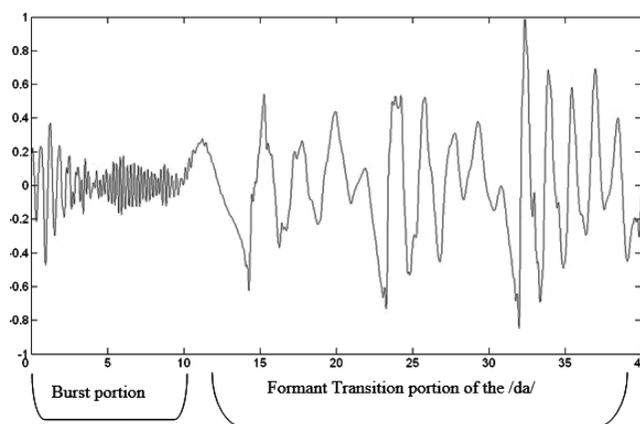


Figure 1. Waveform of the stimulus used in the present study.

instrument which had BIOMARK software (Navigator Pro AEP, Pleasanton, CA 94566 USA). All audiological testing was performed between 9 to 12 a.m. on Saturdays and Sundays (during the weekend).

Test Environment

All objective audiological recordings were carried out in sound treated rooms (ANSI S3.1, 1999). Pure tone and speech audiometry were carried out in a two room audiological setup whereas immittance audiometry, click-evoked ABR, and S-ABR were carried out in a single suit audiological setup.

Statistical Analysis

Statistical analysis of the results was performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, IBM Corp.; New York, USA). The statistical analysis includes descriptive measures, paired t test, and multivariate analysis of variance (MANOVA). The Shapiro-Wilk test was used to check normality of the data and it showed a normal distribution for both groups. Latency peaks of the click-evoked and S-ABRs were marked offline by two experienced audiologists using visual analysis. Since high correlation measures were obtained between the two, only one of them were taken for analysis. Click-evoked ABR latency analysis was done to check the baseline neural response and the absolute and inter-peak latencies were cross-checked against adult normative values.

Detailed latency analysis of the S-ABR was done for the previously established peaks of S-ABR including V, A, D, E, F, and O waves, the same as used by Johnson et al. [16]. Among these waves, the V and A are onset responses whereas C is the marked representation of the transition between an aperiodic consonant to a periodic vowel. The subsequent peaks D, E, and F are frequency following responses (FFR). These peaks correlate to the formant frequencies of the vowel portion of the /da/ stimuli. Latencies of these peaks were marked with the corresponding letter based on the existing literature. Wave O correlates to the temporal offset of the stimulus [17].

RESULTS

The paired t-test results revealed no significant differences between the two ears at 0.05 significance levels. Hence, data from both ears was

Table 2. Stimulus and acquisition parameters for click and speech-evoked ABR

Stimulus	Click evoked ABR	Speech-evoked ABR
Duration	100 μ s	40 ms
Intensity	90 dBnHL	80 dB SPL
Polarity	Rarefaction	Rarefaction
Repetition rate	11.1/s	10.9/s
No. of sweeps	1500	3000
Analysis time	10 ms	64 ms
Pre stimulus time	2 ms	10 ms
Filter setting	100–3000	100–2000
Electrode placement	Non inverting: vertex	Non inverting: vertex
	Inverting: test ear mastoid	Inverting: test ear mastoid
	Ground: opposite mastoid	Ground: opposite mastoid
Transducers	Insert earphone (ER-3A)	Insert earphone (ER-3A)

ABR: Auditory brainstem response

combined and analyzed further. Mean and standard deviations were obtained through descriptive measures. The overall mean latency measures of diabetic individuals were higher (prolonged) in comparison to their age-matched non-diabetic counterparts (Table 3). Sample waveforms of S-ABR for non-diabetic individuals and individuals with diabetes mellitus are given in Figures 2 and 3. Similarly, sample waveforms of the click-evoked ABR for non-diabetic individuals and individuals with diabetes mellitus are given in Figures 4 and 5.

MANOVA was used for within and between group comparisons for the latency measures of waveforms V, A, D, E, F, and O. The results revealed that there were significant differences between two groups for the latencies of wave V [F (1, 41)=65.74; p=0.00; partial eta squared=0.62]; wave A [F (1, 41)=32.01; p=0.00; partial eta squared=0.44]; wave D [F (1, 41)=12.102; p=0.001; partial eta squared=0.23]; wave

Table 3. Mean values of the latencies of various speech-evoked ABR waves in non-diabetic and diabetic subjects (ears combined)

Peaks	Non-diabetic n=11 (22 ears)		Diabetic n=11 (22 ears)	
	Mean	SD	Mean	SD
V	6.57	0.49	7.9	0.58
A	7.79	0.77	8.97	0.59
D	24.10	1.28	25.49	1.06
E	32.12	1.39	34.79	1.57
F	40.06	1.38	43.77	1.32
O	48.61	1.14	50.36	1.09

*n: number of ears; SD: Standard deviation; ABR: Auditory brainstem response

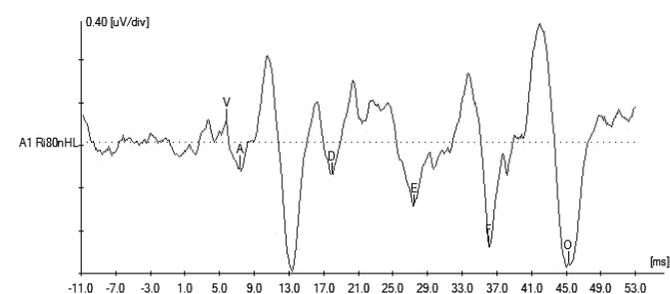


Figure 2. Sample waveform of speech-evoked ABR of a non-diabetic individual. ABR: Auditory brainstem response

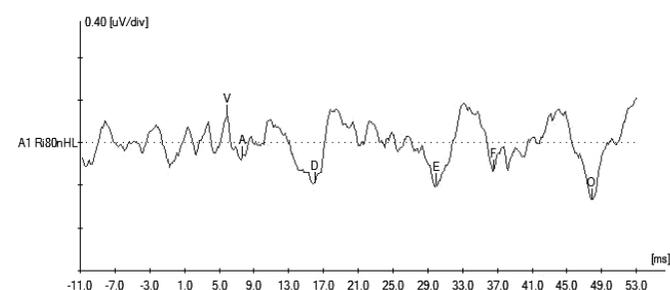


Figure 3. Sample waveform of speech-evoked ABR of an individual with diabetes mellitus. ABR: Auditory brainstem response

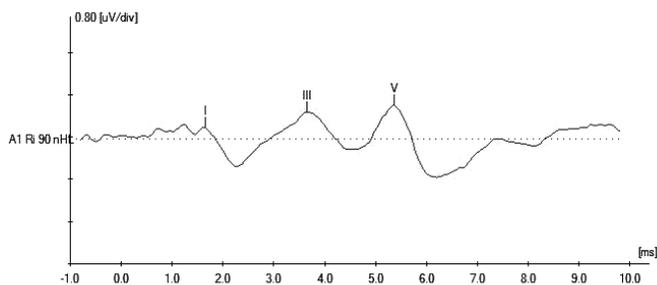


Figure 4. Sample waveform of click-evoked ABR of a non-diabetic individual. ABR: Auditory brainstem response

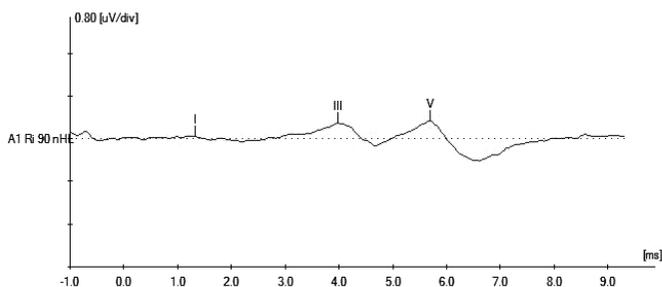


Figure 5. Sample waveform of click-evoked ABR of an individual with diabetes mellitus. ABR: Auditory brainstem response

E [F (1, 41)=34.995; p = 0.00; partial eta squared=0.46]; wave F [F (1, 41)= 60.116; p=0.00; partial eta squared=0.59]; and wave O [F (1, 41)=26.096; p=0.00; partial eta squared= 0.38].

DISCUSSION

The preliminary findings of this study revealed significant abnormal brainstem encoding deficits in individuals with diabetes mellitus type 2 that consisted of both transient and sustained measures of S-ABR. In spite of having normal hearing sensitivity revealed by pure tone thresholds, diabetic individuals have higher auditory processing deficits as a subclinical complication of the disease. One of the most common pathophysiologies noted in the peripheral auditory system is pathogenic changes to microvasculature and sensory nerves [24]. Some of the changes that have been reported through post-mortem studies are thickening of the stria vascularis capillaries, [25] thickened walls of the vessels of the basilar membrane, loss of outer hair cells in the lower basal turn, demyelination of the eighth cranial nerve, and a narrowing of the internal auditory artery [26]. These results may reveal an early susceptibility of peripheral hearing impairment as a pathological advance with the time.

Involvement of the higher auditory structures is evident through transient brainstem responses in individuals with diabetes mellitus in spite of having hearing thresholds within the normal range, suggesting that these deficits cannot be explained by peripheral hearing dysfunctions [5]. Findings of the present study are well supported by the existing literature [14] and adds that both transient and sustained auditory responses are affected in the clinical population of diabetes mellitus.

Effect of Diabetes on Transient Measures (wave V, A, and O) of Speech-Evoked ABR (S-ABR)

The latency of wave V in S-ABR has been measured as the synchronized response to the onset of stimulus and it is similar to the wave V elicited in click-evoked ABR. The /da/ stimulus contains a broader frequency range; hence, it elicits a huge negative-going peak termed as wave A [16, 17]. Previous investigations using the click-evoked ABR suggests clear evidence of prolonged latencies of wave V in diabetes mellitus [5, 13].

In the earliest ABR investigations in diabetic individuals, Donald et al. [13] found significant prolongation of wave III and V in spite of normal latencies of wave I and II [13]. This finding suggests that, even though the eighth nerve transmission is normal, the delay in wave III and V correlates to the transmission delay at the inferior collicular level, probably from the brainstem to midbrain. Histopathological findings of the higher order structures in long term diabetic individuals shows diffuse degeneration of ganglion cells and nerve fibers at the brainstem and cortical levels [27]. These findings may justify the abnormal neural transmission delay at the brainstem level. The finding of this earlier study has been supported by subsequent ABR investigations in diabetes mellitus [5, 6, 13, 14]. Even though some of the authors suggested a dual pathological mechanism, including silent infarct and metabolic disturbances as the explanations of these findings, [14] he delayed onset response to speech stimulus revealed by the current study can also be attributed to these pathological changes in the auditory brainstem.

The delay in the offset response (wave O) also reveals significant deficiency in the synchronized response at the end of the stimuli. The neural cells that encode the offset responses are shown to be in the inferior colliculus [28]. Increased temporal offset may also relate to the pathogenesis in these cells associated with the subclinical complications of diabetes. In addition to the above mentioned consequences of diabetes in the central auditory system, aging can be a contributing factor to these neural delays. Some authors have suggested the increased offset response as a clinical correlate of poor temporal resolution in elderly adults [29].

The current study is the one among a few preliminary investigations using speech stimuli to assess the transient auditory neural responses. Since the speech stimuli is more relevant to audition, the delayed response to it has some implications in the auditory processing deficits in diabetic individuals.

Effect of Diabetes on Sustained Measures of Speech-Evoked ABR (wave D, E, and F)

The sustained measures of S-ABR are important because they correlate to the fundamental frequency (F0) and its first and second harmonics (F1 and F2) representations in the brainstem. [30] These frequency following responses (FFR) do not seem to be affected due to various disorders in spite of delayed transient responses [18]. However, latency analysis of the FFR in diabetic individuals was shown to be prolonged along with the onset and offset representations (V-A complex and O, respectively). This suggests abnormal temporal phase-locking properties to the fundamental frequency and its harmonics of the voiced (vowel) portion of the /da/ stimuli. This may relate to the neural deficiency of the brainstem level as brainstem cells are responsible for originating these responses [30].

Recent investigations towards the aging effect on S-ABR have been suggestive of delayed FFR responses along with altered onset and offset responses^[29]. The authors have attributed these changes to the decreased ability of brainstem level neurons to phase-locking the fundamental frequency components of the stimuli. The mean latency measures of non-diabetic adults obtained in the current study (Table 3) are in agreement with the latency findings of older adults in the study by Vander Werff and Burns^[29]. Hence, the authors of the present study hypothesize that prolonged latency measures in diabetic individuals may be a consequence of the diffused brainstem pathogenesis in this clinical population, rather than aging.

These findings suggest that middle-aged individuals with long-term diabetes complications have a reduction in synchronous firing in response to onset of speech stimuli along with its sustained portion. Since a significant effect of aging on auditory temporal processing can be seen as early as in the middle-aged group, the clinical population of diabetes mellitus have an increased susceptibility to these deficits. Considering diabetes is one of the more common metabolic disorders in the middle aged Indian population, the findings of the present study can have significant clinical implications. Before implementing the above findings, further investigations on a larger sample size and correlation with behavioral temporal measures need to be established. S-ABR can be a promising tool to assess the neural encoding of diabetes mellitus and other metabolic diseases.

CONCLUSION

The study was a preliminary investigation to assess neural encoding of auditory speech stimuli at the brainstem level in individuals with diabetes mellitus type II. As the findings correlated with existing click-evoked ABR findings in diabetic individuals, the utility of S-ABR as a tool in this clinical population has been established. Differences in the groups were significant in terms of onset and offset responses to the stimuli and temporal and phase-locking properties of the sustained portion of the stimuli, including fundamental frequency and its harmonics, in spite of having normally assessed peripheral functions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of All India Institute of Speech and Hearing, Mysore-6, Karnataka, India.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.K.; Design - H.K.S., A.M.; Supervision - P.K.; Resources - P.K., H.K.S.; Materials - H.K.S., A.M.; Data Collection and/or Processing - H.K.S., A.M.; Analysis and/or Interpretation - P.K., H.K.S.; Literature Search - H.K.S., A.M.; Writing Manuscript - H.K.S., A.M.; Critical Review - H.K.S., A.M., P.K.

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