

Auditory Brainstem Response Differences in Diabetic and Non-diabetic Veterans

Nancy Vaughan*
Kenneth James*†
Daniel McDermott*
Susan Griest*†
Stephen Fausti*

Abstract

A number of studies have found statistically significant delays in auditory brainstem latencies of patients with diabetes compared with non-diabetic controls. However, the mechanisms ascribed as responsible for the latency differences between diabetic and non-diabetic patients vary among studies, and the latency differences, while significant, are small. In this 5-year prospective study, auditory brainstem response testing was conducted with 416 non-diabetic and 375 diabetic veterans from the Portland Veterans Affairs Medical Center as part of a larger study. Patients with diabetes had significantly delayed latencies of Wave III and V in the right ear and significantly prolonged interpeak I-III and I-V latencies in both ears. Stimulus polarity difference yielded slightly different results. None of the diabetes-related clinical characteristics were associated with the latency differences between the subject groups after accounting for hearing loss and age. Effect size was calculated and clinical significance of these differences is discussed.

Key Words: Auditory brainstem response, latency, diabetes, neuropathy

Abbreviations: ABR = auditory brainstem response; IPL = interpeak latency; JND = just noticeable difference

Sumario

Un número de estudios han encontrado retardos estadísticamente significativos en las latencias auditivas del tallo cerebral en pacientes diabéticos comparados con controles no diabéticos. Sin embargo, los mecanismos atribuidos como responsables de las diferencias en las latencias entre pacientes diabéticos y no diabéticos varían entre estudios, y las diferencias en las latencias, aunque significativas, fueron pequeñas. En este estudio prospectivo a 5 años, se condujeron las pruebas de respuestas auditivas del tallo cerebral en 416 veteranos no diabéticos y 375 diabéticos, del Centro Médico de Asuntos de Veteranos de Portland, como parte de un estudio mayor. Los pacientes con diabetes tuvieron latencias significativamente retardadas para las ondas III y V en el oído derecho, y latencias inter-pico I-III y I-V significativamente retardadas en ambos oídos. Diferencias en la polaridad del estímulo rindieron resultados levemente diferentes. Ninguna de las características clínicas relacionadas con la diabetes se asoció con las diferencias en las latencias entre los grupos de sujetos, luego de considerar la pérdida auditiva y la edad. Se calculó el efecto del tamaño y se discutió el significado clínico de estas diferencias.

*VA National Center for Rehabilitative Auditory Research, Portland Veterans Affairs Medical Center, Portland, OR;
†Oregon Health and Sciences University, Portland, OR

Daniel McDermott, National Center for Rehabilitative Auditory Research, Portland VA Medical Center, 3710 SW US Veterans Hospital Rd., Portland, OR 97239; E-mail: Daniel.mcdermott@va.gov; Phone: 503-220-8262, ext. 57465; Fax: 503-721-1402

This research was supported by the Medical Research Service of Veterans Affairs, Washington, DC, VA # 07-1498, and by the VA National Center for Rehabilitative Auditory Research, Portland, OR.

Palabras Clave: Respuestas auditivas del tallo cerebral, latencia, diabetes, neuropatía

Abreviaturas: ABR = respuestas auditivas del tallo cerebral; IPL: latencia inter-pico; JND = diferencia apenas notable

Diabetes mellitus is a metabolic disorder that has widespread effects throughout the body. The most common complications of diabetes over time are microvascular disorders (retinopathy and nephropathy) and neuropathy (peripheral and central). In general, central neuropathy in diabetic patients is not as well documented as peripheral neuropathy and it appears that central neuropathy develops later than peripheral neuropathy (Biessels et al, 1999). Prolonged auditory brainstem response (ABR) latencies may serve as an indicator of subclinical neuropathy in the central nervous system, because they may occur in the absence of clinical signs of peripheral or central neuropathy (Al-Azzawi and Mirza, 2004; Das et al, 2001; Diaz de Leon-Morales et al, 2005; Fedele et al, 1984).

Auditory brainstem response (ABR) testing is the clinically accepted method of diagnosis of central transmission delays in response to auditory stimuli. This test involves interpretation of average responses recorded from scalp electrodes as continuous waveforms within the first 10 milliseconds after an auditory stimulus is presented by earphones. Certain peaks within these waveforms tend to occur reliably at regular time intervals (Fowler and Mikami, 1992; Schoonhoven, 1992). It is theorized that the time periods between peaks are prolonged or that the absolute latency of the peaks are delayed in diabetic patients due to some diabetic mechanism such as microangiopathy or central neuropathy.

Several studies have found statistically significant delays of ABR latencies in diabetic compared with non-diabetic patients or normal controls (Al-Azzawi and Mirza, 2004; Diaz de Leon-Morales et al, 2005; Lisowska et al, 2001a), but two concerns regarding these differences remain to be clarified. The first is lack of consensus across studies regarding which diabetic mechanisms are associated with the prolonged diabetic ABR latencies. For instance, Bayazit et al (2000) has found that diabetic patients with retinopathy have longer ABR latencies than diabetic patients without retinopathy, and suggested that ABR might be a valuable predictor of the course of retinopa-

thy in diabetic patients. Still other studies have found no association between retinopathy or other diabetic health variables and ABR latencies (Diaz de Leon-Morales et al, 2005; Fedele et al, 1984; Lisowska et al, 2001b).

The second concern is whether these statistically significant latency delays reported in the literature are large enough to be clinically important. The ABR testing reported here is part of a larger study examining the effects of diabetes on auditory function by comparing test results in a large sample of veterans with and without diabetes.

MATERIALS AND METHODS

Participants

This study was conducted at the National Center for Rehabilitative Auditory Research (NCRAR) at the Veterans Affairs Medical Center in Portland, Oregon, from March 1999 to April 2004. All participants who volunteered for the study were patients at the Portland Veterans Affairs Medical Center (PVAMC). Participants were randomly selected from a list of patients seen at the PVAMC who had been diagnosed with diabetes for at least five years, and from an alternative list of PVAMC patients without diabetes. The study was approved by the Portland VA Institutional Review Board (IRB), and all participants signed a written informed consent.

Audiometrics

Pure tone thresholds were obtained at octave frequencies 250 Hz through 8000 Hz and at 10, 12.5, 14 and 16 kHz using a Madsen Orbiter model 322 clinical audiometer. Inter-octave frequencies were tested at 3 and 6 kHz also. Sennheiser circum-aural earphones were used for the high frequency testing beyond 8 kHz.

ABR Procedures

Auditory brainstem response (ABR) testing was conducted using the Intelligent Hearing System SmartEP Version 2.22. The stimuli were broadband clicks presented at 90

dB nHL re: 32 dB SPL through insert earphones. Sequences of 1000 sweeps were presented monaurally, alternating between rarefaction and condensation polarity. Sequences of the same polarity then were added together for the final analysis providing one rarefaction and one condensation sequence in each ear representing two summed rarefaction and two summed condensation responses of 2000 sweeps. The electrode montage utilized Etymotic ER3-26A gold foil wrapped electrode eartips (tiptrodes) at the inverting electrode sites in the ear canal (channel A). In addition, an inverting silver-silver chloride electrode was also placed on the ipsilateral mastoid (channel B) and both channels (A and B) were recorded simultaneously. Both sites were referenced to the forehead (Fz) as the non-inverting electrode, and the contralateral mastoid served as the ground. The clicks were 100 μ seconds in duration with a rectangular window and were presented at a rate of 7/second. Responses were band pass filtered on line with a high pass frequency of 30 Hz and a low pass cutoff of 3000 Hz.

Additional audiometric tests were conducted in the same four- to five-hour session as part of the larger study exploring the association between diabetes and audiometric function (Virtaniemi et al, 1993).

Diabetes Tests

A small sample of blood from a finger prick was taken on the day of the experimental session to obtain a measure of blood glucose levels and metabolic control (HbA1c) at the time of test. The HbA1c test measures the percent of glycosylated hemoglobin in the blood and reflects the metabolic state over the past three months. The blood tests were done with an Accucheck blood glucose meter. During the same test session, a WR Medical Electronics CASE IV™ (Computer Aided Sensory Evaluator) system was used to test for peripheral neuropathy by measuring sensitivity to cooling and to vibration on the upper surface of one foot. Sensitivity is measured in units of just noticeable differences (JND) between levels of pressure for vibration sensitivity (JNDvib) and between levels of temperature for cooling sensitivity (JNDcool). The CASE IV™ unit uses 25 levels of stimulation based on an exponential JND scale for both the vibration and the cooling stimuli. A larger JND indicates decreased

sensitivity requiring larger differences in stimulus levels in order for a change to be detected by the participant. This test of peripheral neuropathy is called quantitative sensory testing (QST).

Retinopathy and nephropathy use of insulin data were obtained from the electronic medical records, and duration of diabetes calculated from the date of diagnosis entered in the medical record.

Statistical Analysis

The comparability of demographic and diabetes-related characteristics between those with and without ABR data were tested using the t-test for continuous variables and Chi-square test for categorical variables. P-values were not adjusted for multiple comparisons.

Regression analyses were performed to determine which of the demographic and diabetes-related variables listed in Table 1 were significant factors in predicting absolute ABR latencies and inter-peak latency (IPL) differences. Age, hearing loss and subject group (diabetic, non-diabetic) were considered important predictor variables and were forced into the model for each absolute latency and IPL. Each of the remaining variables was entered in a step-wise fashion to determine its contribution to the prediction of absolute latencies or IPLs. Only those variables that were common to both diabetic subgroups were used; insulin use and duration of diabetes were not included. Twelve models were constructed for each left/right ear, condensation/rarefaction combination of absolute latencies and another 12 models were constructed for each left/right ear, condensation/rarefaction combination of IPLs (2 ears x 2 polarities x 3 ABR peaks). Normality of the absolute latencies and IPLs were verified. Each of the models produced least squares estimates of the diabetic/non-diabetic group means and these were assessed to determine the clinical significance of differences that were statistically significant. Between-group differences were compared to the error standard deviation to provide an estimate of the between-group effect size.

RESULTS

A total of 791 patients were tested for the overall study over a five-year period. The

Table 1. Means and standard deviations within the diabetic group for age, hearing loss (PTA) and for each diabetes-related variable by presence or absence of ABR data. PTA = pure tone average of 1000, 2000, 3000, and 4000 HZ.

Variable	Group	N	Mean (SD)	P- value
Age (years)	ABR	257	61.0 (9.6)	.499
	NO_ABR	114	61.7 (9.4)	
PTA Left (dB HL)	ABR	255	37.1 (18.4)	.242
	NO_ABR	102	40.0 (21.5)	
PTA Right (dB HL)	ABR	255	35.7 (18.6)	.245
	NO_ABR	102	38.5 (21.2)	
Diabetes-related Variables				
Glucose (ml/dl)	ABR	255	212.4 (83.6)	.592
	No_ABR	111	207.3 (84.5)	
Hemoglobin A1c (%)	ABR	248	7.8 (1.5)	.137
	No_ABR	110	8.1 (1.7)	
JNDcool	ABR	237	15.7 (5.9)	.567
	No_ABR	98	15.3 (5.5)	
JNDvib	ABR	228	21.2 (3.4)	.891
	No_ABR	95	21.1 (3.7)	
Kidney Problems	ABR	*105 (42.5%)		.952
	No_ABR	43 (42.2%)		
Retinopathy	ABR	*72 (35.1%)		.977
	No_ABR	22 (34.9%)		

*N (%) represents the number (expressed also as a percentage) of patients with available kidney and retinopathy data who had recorded kidney and retinopathy problems.

average age was 61.8 years (SD = 10.3) and age range was 25 to 83 years. Of the total number, 375 (47.4%) were diabetic and 416 (52.6%) were non-diabetic patients. Twenty of the non-diabetic patients and seven of the diabetic patients were female. Average duration of diabetes from diagnosis to date of test was 12.5 years (SD 8.7 years) and less than half of the diabetic patients (44%) were taking insulin. Others were controlling their diabetes by diet and/or oral medication.

From the total number tested, ABR data were obtained for approximately 75% of the sample (n=587). There was no scorable ABR data for just over one-quarter of the total number (n=204) and this was primarily due to severe hearing loss (55%). A smaller percentage of these data also was missing because of difficulties experienced by the patients – restlessness or inability to cooperate with the test requirements, and a still smaller number lost due to equipment failure. An additional six patients were excluded because their pertinent data could not be retrieved from the original files for this analysis, leaving data from 581 patients available for ABR analysis. Of the original 791 participants, 90 of the 416 (21.6%) non-diabetic patients and 114 of the 375 (30.4%) diabetic patients had no ABR data.

Characteristics of Patients with Missing ABR Data

A series of t-tests showed no statistically significant differences in age or hearing loss or in any of the diabetes-related health variables between diabetic patients who had ABR data and those who did not (see Table 1). Within the non-diabetic subject group, on the other hand, patients with no scorable ABR data were about 5 years older and had about 15 dB more hearing loss than the non-diabetic patients who had at least one scorable ABR wave (see Table 2). A series of t-tests showed those differences to be statistically significant, and the differences are also clinically important. Non-diabetic patients with no scorable ABR data also had significantly higher average peripheral neuropathy scores, but the differences were small and not likely to be clinically significant. In summary, non-diabetic patients from whom no scorable ABR data were obtained were older and had more hearing loss than those from whom at least some ABR waveforms were obtained. Among diabetic patients, however, there were no significant differences in clinical data or in age and hearing loss between those with and without ABR data.

Participants from whom ABR data was obtained did not differ significantly in age

Table 2. Means and standard deviations within the non-diabetic group for age, hearing loss (PTA) and for each diabetes-related variable by presence or absence of ABR data. PTA = pure tone average of 1000, 2000, 3000, and 4000 HZ.

Variable	Group	N	Mean (SD)	P- value
Age (years)	ABR	326	61.4 (11.1)	<0.001
	No_ABR	90	66.0 (9.2)	
PTA Left (dB HL) (1,2,3,4 kHz)	ABR	322	33.2 (17.7)	<0.001
	No_ABR	90	50.3 (24.7)	
PTA Right (dB HL) (1,2,3,4 kHz)	ABR	323	31.9 (18.6)	<0.001
	No_ABR	90	46.9 (24.8)	
Diabetes-related Variables				
Glucose (ml/dl)	ABR	325	104.4 (20.1)	.331
	No_ABR	90	106.7 (19.5)	
Hemoglobin A1c (%)	ABR	324	5.5 (0.48)	.401
	No_ABR	90	5.4 (0.77)	
JNDcool	ABR	296	13.0 (5.2)	<0.001
	No_ABR	83	16.1 (6.0)	
JNDvib	ABR	307	19.3 (3.3)	.007
	No_ABR	82	20.4 (3.2)	
Kidney Problems	ABR	4 (1.3%)		.161
	No_ABR	3 (3.7%)		
Retinopathy	ABR	0 (0.0%)		
	No_ABR	0 (0.0%)		

*N (%) represents the number (expressed also as a percentage) of patients with available kidney and retinopathy data who had recorded kidney and retinopathy problems.

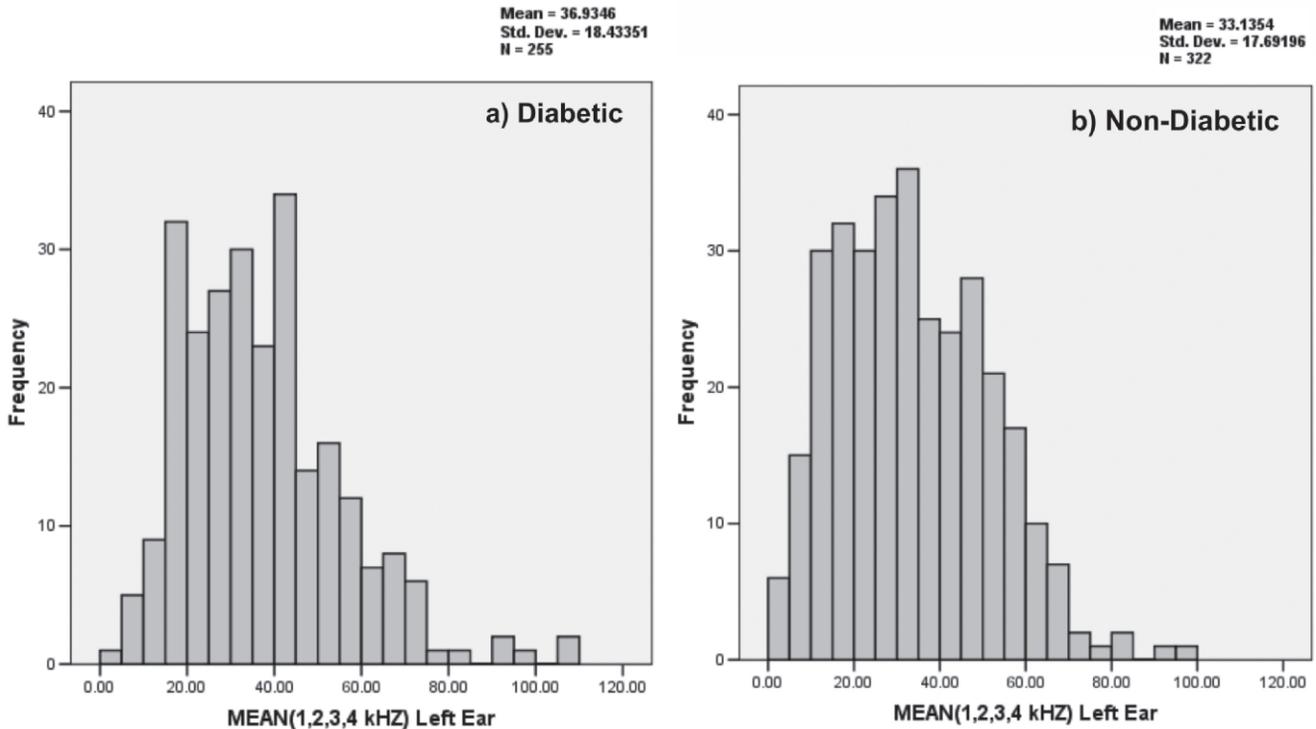


Figure 1. Frequency distributions of PTA4 (1000, 2000, 3000, 4000 Hz) in the left ear for diabetic participants (a) and non-diabetic participants (b).

($F=.205$, $p=.651$) between the two subject groups (diabetic, non-diabetic); however, there were significant differences in four-frequency (1000, 2000, 3000, 4000 Hz) pure tone averages (PTA4) between diabetic and non-diabetic subjects for

each ear adjusted for age (Right ear: $F=7.849$, $p<.05$; Left ear: $F=10.06$, $p<.05$). Figure 1 (a and b) shows histograms of left ear PTA4 for each subject group.

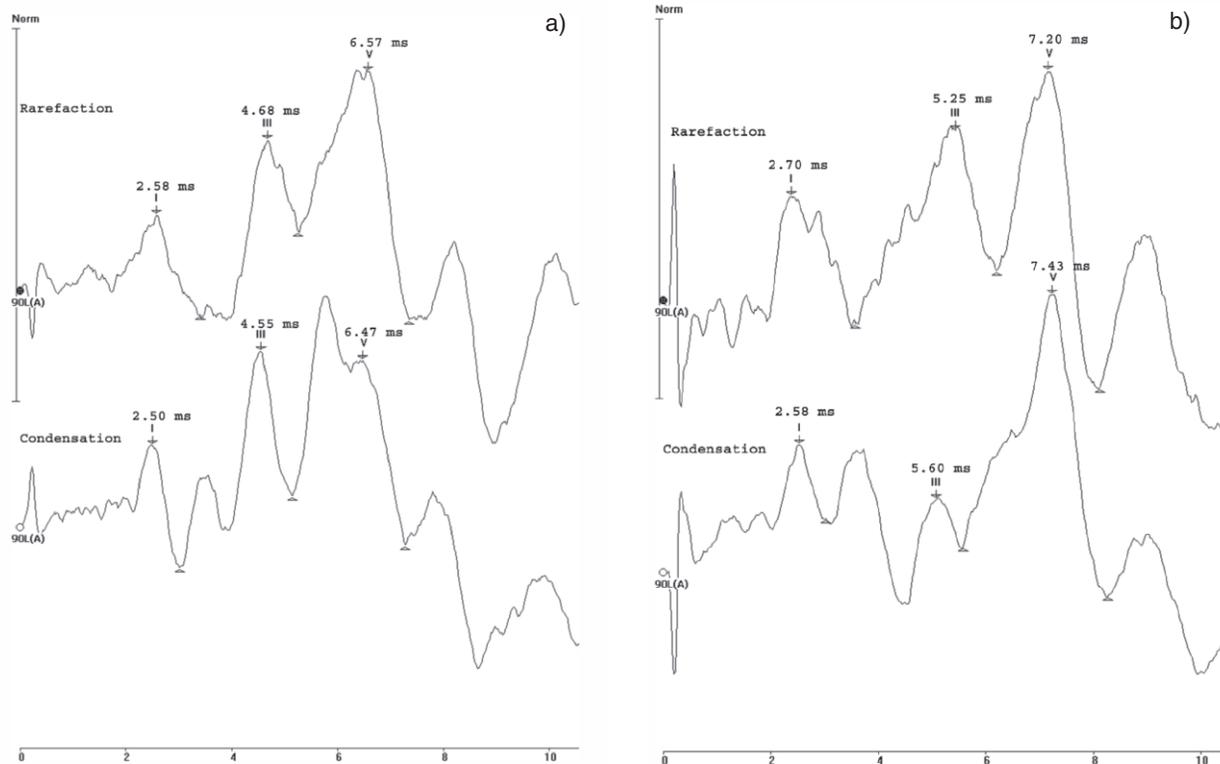


Figure 2. *a:* Non-diabetic waveform auditory brainstem responses, left ear, rarefaction (top) and condensation (bottom) at 90 dB nHL. *b:* Diabetic waveform auditory brainstem responses, left ear, rarefaction (top) and condensation (bottom) at 90 dB nHL

ABR Latencies

Three peaks (Waves I, III, and V) were identified in each of the ABR recordings when possible. In the case of a bifid IV-Vpeak, the second peak was marked if it occurred between five and eight milliseconds. The range for Wave I was restricted to 1.2 to 3 milliseconds and Wave III was marked as the most prominent peak between Wave I and Wave V. The examiner marked the peak which was then reviewed by the principal investigator. If there was disagreement, both observers reviewed the recording together and made a decision. Figure 2 shows examples of auditory brainstem response traces from a non-diabetic and a diabetic participant.

Regression analyses indicate that absolute latencies of all three peaks (I, III, V) were significantly different between the two subject groups in the right ear only: specifically Wave III and Wave V are prolonged in diabetic patients using condensation polarity and Wave I is prolonged in the

non-diabetic group using rarefaction clicks. The I-V interpeak latencies (IPL) were significantly prolonged in the diabetic group in both ears with both stimulus polarities. The I-III IPLs obtained with condensation clicks were prolonged in both ears in diabetic patients, and the III-V IPLs obtained with rarefaction clicks were prolonged only in diabetic left ears. The actual latency differences although statistically significant, were small (-.06 to .13 ms). These results are summarized in Table 3 which shows all conditions for which diabetic patients had prolonged latencies compared with non-diabetic patients.

The p-values for age and hearing loss effects in this model are shown in Table 3 also. Both age and hearing loss (PTA4) were significant factors in all three of the absolute latency conditions ($p < .0001$) in the right ear. The correlation between age and hearing loss was only moderate ($r = .49$, right ear; $r = .52$, left ear) and both factors contributed independently to the absolute latency differences between the two subject groups. Age

Table 3. Results of a series of regression analyses with each of the absolute and interpeak latencies as dependent variables. This table reports results only for those latencies which were significantly different between subject groups (diabetes, non-diabetes). Estimated least square means and standard errors are reported with the effect size and p-values for subject group, and the p-values for age and hearing loss. Other independent variables in these regression models included diabetes-related variables from Tables 1&2.

Absolute Latency	Ear	Polarity	Non-Diabetic		Diabetic		Subject Group Effect Size ²	Subject Group p-value	Age p-value	Hearing Loss p-value
			n	LSM±SE ¹	n	LSM±SE				
I	Right	Rarefaction	212	2.67±.01	147	2.61 ± .02	-0.28	0.010	0.020	<0.001
III	Right	Condensation	219	4.88±.02	172	4.99 ± .03	0.32	0.002	0.004	<0.001
V	Right	Condensation	219	6.92±.02	172	7.04 ± .03	0.32	0.001	<0.001	<0.001
Interpeak Latency										
III-V	Left	Rarefaction	185	1.91±.02	145	1.97 ± .02	0.24	0.035	0.960	0.797
I-V	Left	Rarefaction	157	4.23±.03	126	4.36 ± .03	0.38	0.002	0.951	0.065
I-III	Left	Condensation	121	2.28±.02	97	2.38 ± .02	0.43	0.002	0.185	0.152
I-V	Left	Condensation	130	4.30±.03	108	4.41 ± .04	0.31	0.019	0.646	0.056
I-III	Right	Condensation	161	2.27±.02	121	2.37 ± .03	0.35	0.004	0.020	0.608
I-V	Right	Condensation	181	4.26±.03	129	4.38 ± .03	0.35	0.003	0.004	0.474

¹Least Squares Mean ± Standard Error

²Effect Size = Difference in LSM between groups/Error Standard Deviation

was a significant factor in interpeak differences only in the right ear IPLs with condensation clicks, but hearing loss was not significant in any of the interpeak differences.

Two diabetes health variables which were significant were not included in Table 3 because the latencies were not different between the subject groups. High glucose levels were significant ($p=.035$) for III-V IPL differences in the right ear using rarefaction clicks, and HbA1c ($p=.045$) was significant in the left ear Wave V latency using condensation clicks, but these conditions did not include differences between diabetic and non-diabetic latencies. In fact, no pattern was discernible in these analyses regarding the effects of any of the diabetic-related health variables (shown in Table 1) on the ABR latency differences between diabetic and non-diabetic patients.

Effect sizes were calculated for the statistically significant interpeak and absolute latency differences (Table 3) to determine the value of the degree of difference between subject group latencies. Effect sizes ranged from .24 to .43, with most in the range of .30 to .38. The largest effect size, .43, was for the prolonged diabetic I-III IPL in the left ear using condensation clicks.

A series of regression analyses was conducted in diabetic patients only to determine if diabetes-related variables were predictive of IPL differences or prolonged ABR latencies.

Insulin (yes, no) and duration of diabetes were added to the diabetes-related variables for these analyses. Age and hearing loss were forced into the model and the remaining variables competed stepwise. Each IPL and absolute latency condition (ear, polarity) served as the dependent variable in a series of regression models. Although age and hearing loss accounted for a significant amount of variability in each of the absolute latency conditions, there was no consistent pattern of involvement of diabetic health mechanisms in the interpeak or absolute latency differences within the diabetic patients.

CONCLUSIONS AND DISCUSSION

The data reported here are from a larger study comparing various auditory functions between diabetic and non-diabetic veterans. About 20% of non-diabetic patients and 30% of diabetic patients did not generate ABR data. Age and hearing loss were significantly higher in the non-diabetic patients with no ABR data. This was not unexpected since both factors are known to affect ABR latencies (Fowler and Mikami, 1992; Chandrasekhar et al, 1995), but we were unable to explain the differences among the diabetic patients who did and did not generate ABR data. Neither age, hearing loss, nor any of the diabetes-related health variables were statistically different between the ABR and No_ABR groups in the diabetic patients. Perhaps other comorbid

health conditions such as cardiac and vascular conditions commonly associated with diabetes may have contributed to the absence of ABR responses or may have masked ABR responses in diabetic patients.

In those patients with scorable ABR data, statistically significant mean latency differences were found between diabetic and non-diabetic patients, even after adjusting for age, hearing loss and a series of diabetic-related variables in the regression models. Since ears and polarity effects were examined separately, our findings suggest that condensation polarity may be more sensitive than rarefaction to absolute and interpeak latency differences between diabetic and non-diabetic populations. However, regardless of stimulus polarity, when latencies were significantly different between the groups, age and/or hearing loss were the only significant covariates. None of the diabetes-related characteristics was predictive of either absolute or IPL latency differences. Neither was there any consistent pattern of significant diabetic-related variables associated with significant latency differences within the diabetic patients.

The association of ABR latencies with diabetes-related health variables has been inconsistent throughout the literature. A number of studies have found a variety of diabetes-related clinical characteristics associated with these neural transmission delays in the brainstem. Bayazit et al (2000) found that diabetic patients with retinopathy had longer latencies than those without microvascular complications, but Lisowska et al (2001b) was unable to find an association between microangiopathy and ABR latencies and suggested that the prolongations may be due to diabetic changes in cochlear and retrocochlear mechanisms due to the metabolic environment. Virtaniemi et al (1993) investigated the effects of glucose levels on ABR latencies with increased insulin dosages. While the glucose levels were lowered significantly, no change was found in the ABR latencies. Delayed latencies and IPLs in diabetic patients were independent of peripheral neuropathy, retinopathy or nephropathy in a recent study by Diaz de Leon-Morales et al (2005). Al-Azzawi and Mirza (2004) also further found that delayed diabetic latencies compared with healthy controls were not associated with type or duration of diabetes. Apparently, the only consistent findings have been those of prolonged ABR latencies in diabetic patients, the reasons for which have yet

to be explained.

Regarding prolonged latencies in diabetic populations, examination of the magnitude of these latency prolongations compared with non-diabetic populations raises yet another question. Although the reported differences have been statistically significant, none of the group latency differences in the current study was greater than .13 ms. Differences between diabetic and non-diabetic latencies in other studies are also small, although the mean latencies reported in the current results are the estimated least square means from the regression models, they may be more accurate because the covariates have been accounted for.

Studies have shown that Wave V interaural latency differences greater than .2 ms are sensitive to retrocochlear pathology (Chandrasehkar et al, 1995; Gordon and Dohen, 1995). One study found that specificity to acoustic neuromas using a greater than .3 ms interaural difference (Gstoettner et al, 1992), but the current authors were unable to find any general agreement regarding what constitutes a clinically significant latency difference between individuals or groups. In this study, we used effect sizes to estimate what a clinically important difference. As shown in Table 3, these ranged in absolute value from 0.28 to 0.43. Cohen (1988) provides a discussion of effect sizes and their clinical implications and considers those that we observed to be small to medium in the context of a variety of medical disciplines. In our sample, approximately 75 percent of the observations in the two subject groups would be expected to overlap. Thus, although we observed statistically significant differences between the two patient groups, from a clinical standpoint these differences may not be particularly important.

The trend for slightly longer ABR latencies and IPLs in diabetic patients has been seen in a number of studies. The effects of diabetes are widespread and insidious, but at this point the effects on ABR latencies, although statistically significant, are small and may indicate subclinical diabetic central neuropathy or subclinical auditory processing disorders in diabetic patients which are not apparent in behavioral test results. The NCRAR is currently conducting another study to investigate the effects of diabetes on the ability to process verbal information.

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