Effects of Diabetes Mellitus Type I with or without Neuropathy on Vestibular Evoked Myogenic Potentials

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Received: 30 Dec. 2011; Received in revised form: 10 Dec. 2012; Accepted: 4 Jan. 2013

Abstract- Diabetes mellitus type I is a metabolic disorder that affects multiple systems including the inner ear. Patients with diabetes mellitus commonly complain about dizziness, floating sensation, tinnitus and sweating. The aim of this study was to compare vestibular evoked myogenic potentials (VEMPs) between diabetic patients with or without neuropathy. Subjects included 14 patients with diabetes mellitus type I with polyneuropathy, 10 patients with diabetes mellitus type I without polyneuropathy and 24 healthy volunteers. Range of age in participants was 15-40 years old. The VEMPs were recorded with 500 Hz tone bursts with intensity at 95 dB. There was statistically significant difference between the groups in P13 and N23 latencies (P<0.05). There was no statistically significant difference between groups in absolute and relative amplitudes. Prolonged latencies of the VEMP suggest lesions in the retrolabyrinthine, especially in the vestibulospinal tract.

Acta Medica Iranica, 2013; 51(2): 107-112.

Keywords: Diabetes mellitus type I; Saccule; Sternocleidomastoid muscle; Vestibular evoked myogenic potentials; Vestibular System

Introduction

Diabetes mellitus is a group of metabolic diseases in which blood glucose level rises. The two most common types of diabetes mellitus are diabetes mellitus type I and type II (1). Diabetes mellitus is characterized by abnormal metabolism of carbohydrate, fat and protein resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs especially the eyes, kidney, nerves, heart and blood vessels (2).

Most researchers believe that diabetes can cause different pathologies in humans (3-7). Bittar *et al*. report that glucose metabolism significantly influence the physiology of inner ear which is very active metabolically (2). The inner ear doesn't store energy, therefore minor variations in blood glucose affect its function and cause balance disorder (2). Patients with diabetes mellitus commonly complain about dizziness, floating sensation, tinnitus, weakness and sweating (3-7). However, studies in this area are very limited. Although it is known that diabetes affects many organ systems in the body and diabetic patients have vestibular problems, it is not yet clear which part of the vestibular system is the most affected part. On the other hand, in most cases in patients with diabetes, the balance of the system is evaluated using electronystagmography (ENG). Rigon *et al.* evaluated the vestibular system in patients with diabetes mellitus type I using ENG and their results showed that diabetes can affect the vestibular organ, even if there are no otoneurologic complaints (8). Other studies have shown that the range of vestibular organ impairment in diabetes mellitus type I seems to depend mainly on the presence and character of hypoglycaemic incidents and the duration of the disease (9). ENG only considers semicircular canals and superior vestibular nerve. While by using vestibular evoked myogenic potentials (VEMP) test, the examiner is able to assess

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otolith organs of the vestibular system especially the saccule and inferior vestibular nerve. VEMP reflects vestibular system activity that is elicited by high-intensity sounds and detected as a change in muscle potentials within the neck. High intensity abrupt sounds, such as clicks or short tone bursts, activate the saccule, an otolith organ within the vestibular apparatus in the inner ear. Stimulation of the saccule generates a response from corresponding vestibular nucleus, with projections then to the spinal cord and then innervation of the sternocleidomastoid muscle (SCM), an anterior (strap) neck muscle. VEMPs do not reflect contraction of the SCM muscle but, rather, an alteration in tonic status of the muscle. The VEMP appears as a biphasic (positive and negative) response in the latency region 10 to 25 ms. The first wave of the contract, P1 or P13 and the second wave is shown as N1 or N23 (10).

Studies of VEMP in diabetes are very limited. In a study carried out by Bektas *et al*. in 2008, VEMP responses were found to be normal in NIDDM (non-insulin-dependent diabetes Mellitus) patients with or without polyneuropathy (11). Several studies showed that in patients with type I diabetes, peripheral and central vestibular system can also be changed (4,9,12,13). Because of the high number of individuals with diabetes mellitus worldwide (4.6%)(8), there is a growing concern among health professionals to avoid possible secondary disorders caused by diabetes, which may impact the quality of life in these individuals. The aim of this study was to compare vestibular evoked myogenic potentials (VEMPs) between diabetic patients with or without neuropathy.

Materials and Methods

This study is a comparative cross-sectional study. 14 patients with type I diabetes mellitus without polyneuropathy (6 female and 8 male), 10 diabetic patients with type I diabetes mellitus with polyneuropathy (4 female and 4 male) and 24 healthy volunteers (13 female and 11 male) were enrolled in this study.

All patients were examined by otoscopy and audiometric testing before the study. Subjects with abnormal audiometric tests (average hearing loss worse than 25 dB on frequencies 500, 1000 and 2000 Hz) and limitation of neck movements were excluded from the study.

The presence of PNP was diagnosed by detection of nerve conductance velocity abnormality in at least two nerves, one of which must be the sural nerve. According to the test results, diabetic patients were divided into PNP^+ and PNP^- groups (14).

After appropriate skin cleaning, surface electrodes were placed on the following positions: active, on the upper one-third of SCM; reference electrode, on the anterior margin of ipsilateral clavicle; and ground electrode, on the forehead. VEMP recordings were performed with evoked potentials machine (Bio-Logic model, Natus, US). The tone burst (500 Hz) with intensity of 95 dB, rarefaction polarity and a repetition rate of 5.1/sec was delivered through insert earphone ER-3A and vestibular evoked myogenic potential was recorded. Stimuli were presented to ipsilateral. Acquisition parameters include: the amplifier gain×5000, analysis time 100 ms and filter with bandwidth of 10-1500 Hz. Absolute amplitude was the magnitude of the voltage between the positive and negative set of P13-N23 [equal distance between peak to through of the two VEMP components (P1 to N1 or P13 to N23)].

Data were processed using SPSS version 12. In order to compare the means, if variances were homogeneous, we used one-way ANOVA, and If variances were inhomogeneous Welch analysis of variance were used for statistical analysis. Statistical significance level was set at $P<0.05$.

Results

Forty-eight subjects received a total of 96 VEMP tests. The mean peak latency of P13 was statistically significant difference between groups ($P=0.001$ in right ear and $P=0.003$ in left ear) (Table 1). Also the mean peak latency of N23 was statistically significant difference between groups ($P=0.002$ in right ear and $P=0.02$ in left ear) (Table 2). There was no significant difference between the mean absolute amplitudes of the three groups ($P=0.47$ in right ear and $P=0.28$ in left ear) (Table 1). Also there was no significant difference between the mean relative amplitudes of the three groups ($P=0.31$) (Table 2). The mean peak latency of P13 was statistically significant difference between DM with neuropathy group and normal group ($P<001$ in right ear and $P=0.001$ in left ear) (Table 3). Also The mean peak latency of N23 was statistically significant difference between DM with neuropathy group and normal group ($P<001$ in right ear and $P=0.002$ in left ear) (Table 4).

Table 1. ANOVA: comparison P13 between groups (normal subjects and diabetic patients with or without polyneuropathy).

		Mean	Standard deviation	F	*P*-value
Right Latency P13	Normal (n=24)	14.67	0.69	8.82	0.001
	DM with PNP (n=10)	16.29	1.70		
	DM without PNP (n=14)	14.96	0.9		
Left Latency P13	Normal (n=24)	14.61	0.73	6.78	0.003
	DM with PNP (n=10)	16.11	1.74		
	DM without PNP (n=14)	15.05	1.00		
Right Amplitude	Normal (n=24)	211.55	75.17	0.755	0.476
	DM with PNP (n=10)	182.88	63.24		
	DM without PNP (n=14)	190.33	65.30		
Left Amplitude	Normal (n=24)	200.95	65.69	1.307	0.281
	DM with PNP (n=10)	164.44	41.21		
	DM without PNP (n=14)	193.34	61.41		

DM: Diabetes mellitus; PNP: polyneuropathy

Table 2. Welch: comparison N23 and Amplitude Ratio between groups (normal subjects and diabetic patients with or without polyneuropathy).

		Mean	Standard deviation	Statistic(a)	d.f.	*P*-value
Right Latency N23	Normal (n=24)	23.06	1.15	8.668	17.326	0.002
	DM with PNP (n=10)	26.92	3.62			
	DM without PNP (n=14)	24.54	1.64			
Left Latency N23	Normal (n=24)	22.98	1.19	4.399	17.355	0.028
	DM with PNP (n=10)	25.22	2.62			
	DM without PNP (n=14)	24.10	2.02			
Amplitude Ratio	Normal (n=24)	0.12	0.07	1.253	17.767	0.310
	DM with PNP (n=10)	0.15	0.12			
	DM without PNP (n=14)	0.19	0.15			

DM: Diabetes mellitus; PNP: polyneuropathy

Table 3. Multiple comparisons: comparison P13 between 2 groups(normal and DM with PNP, normal and DM without PNP, DM with PNP and DM without PNP)

Dependent Variable	Group (I)	Group (J)	Mean Difference (I-J)	Std. Error	*P*-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Right Latency P13	normal	DM without PNP	-0.28887	.34737	0.410	-0.9885	0.4108
		DM with PNP	-1.61858	.38878	<001	-2.4016	-0.8355
	DM without PNP	Normal	0.28887	.34737	0.410	-0.4108	0.9885
		DM with PNP	-1.32971	.42767	0.003	-2.1911	-0.4683
	DM with PNP	Normal	1.61858	.38878	<001	0.8355	2.4016
		DM without PNP	1.32971	.42767	0.003	0.4683	2.1911
Left Latency P13	normal	DM without PNP	-0.44560	.36492	0.228	-1.1806	0.2894
		DM with PNP	-1.50417	.40843	0.001	-2.3268	-0.6816
	DM without PNP	Normal	0.44560	.36492	0.228	-0.2894	1.1806
		DM with PNP	-1.05857	.44929	0.023	-1.9635	-0.1537
	DM with PNP	normal	1.50417	.40843	0.001	0.6816	2.3268
		DM without PNP	1.05857	.44929	0.023	0.1537	1.9635

DM: Diabetes mellitus; PNP: polyneuropathy

Table 4. Multiple comparisons: comparison N23 between 2 groups(normal and DM with PNP, normal and DM without PNP, DM with PNP and DM without PNP).

Dependent Variable	Group (I)	Group (J)	Mean Difference (I-J)	Std. Error	*P*-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Right Latency N23	normal	DM without PNP	-1.48268	0.68025	0.035	-2.8528	-.1126
		DM with PNP	-3.86125	0.76135	<001	-5.3947	-2.3278
	DM without PNP	normal	1.48268	0.68025	0.035	0.1126	2.8528
		DM with PNP	-2.37857	0.83751	0.007	-4.0654	-.6917
	DM with PNP	normal	3.86125	0.76135	<001	2.3278	5.3947
		DM without PNP	2.37857	.83751	0.007	0.6917	4.0654
Left Latency N23	normal	DM without PNP	-1.10851	0.60928	0.076	-2.3357	0.1186
		DM with PNP	-2.22508	0.68191	0.002	-3.5985	-.8516
	DM without PNP	normal	1.10851	0.60928	0.076	-.1186	2.3357
		DM with PNP	-1.11657	0.75013	0.144	-2.6274	0.3943
	DM with PNP	normal	2.22508	0.68191	0.002	0.8516	3.5985
		DM without PNP	1.11657	0.75013	0.144	-.3943	2.6274

DM: Diabetes mellitus; PNP: polyneuropathy

Discussion

The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidney, nerves, heart and blood vessels (1). Type 1 diabetes mellitus individuals may suffer from vestibular organ impairment even if there is no otoneurologic symptom (8). In the present study there was statistically significant difference between groups in P13 and N23 latencies. P13 as well as N23 latency in patients with diabetic neuropathy was higher than normal. N23 latency in patients without diabetic neuropathy was higher than normal participants. The study found that responses were affected in the group with neuropathy more than without neuropathy group. In the only study done by Bektas *et al.*, P13 and N23 latencies were found to be normal in NIDDM (non-insulin-dependent diabetes mellitus) patients with or without PNP (11). Possible reasons for this inconsistency could be due to different patients groups studied. Various authors suggested that microangiopathy (retinopathy, nephropathy, and neuropathy) might be responsible for diabetes-associated altered inner ear function (3,15). It seems that damage only to the vestibular nerve may be insufficient for VEMP latency prolongation beyond the normal range, and brainstem lesions, especially those in the vestibulospinal tract, are required for the prolongation of P13 latency (16). There has also been an increase in latency of P13 in the lower brain stem stroke and multiple sclerosis (17). In 2001 Perez *et al.* (18) demonstrated functional impairment of the vestibular end organ in diabetic rats using short latency vestibular evoked potentials (VsEPs). Prolongation and amplitude decrease of the first wave of VsEPs, which reflects the vestibular part of the inner ear, was reported. Vestibular disturbances due to hyperglycaemia may be central (9) or peripheral (19). It is known that the labyrinthine structures and, especially the stria vascularis, have a very intense metabolic activity and therefore a constant expenditure is necessary to keep proper concentrations of sodium and potassium in the endolymph. Glucose is fundamental for ATP production within the cells and energy supply for the sodium and potassium pump to work properly. As such, the metabolic alterations which involve the glucose metabolism can impair energy supply, altering the concentration of ions in the endolymph and perilymph, causing a change in the labyrinthine electric potentials, initiating dizziness. The lack of glucose as energy source for the sodium and potassium pump generates the endolymphatic hydrops caused by the retention of sodium in the endolymphatic space and a consequent water volume increase in such compartment (20). The inner ear is particularly sensitive to altered blood glucose and insulin levels; the most common symptoms are vertigo, hearing loss, tinnitus and ear fullness, among others. Vascular stria depends on a constant concentration of blood glucose; variations of blood glucose may cause auditory and balance disorders (13). As previously mentioned, Studies that have examined the VEMP in diabetes are very limited. But disturbances in vestibular tests such as ENG in patients with diabetes mellitus, supported the presence of anomalies in the central system (8,9). The results of this study are consistent with reports that used ENG tests. Biurrun *et al.* in 1991 reported abnormal ENG

results in 50% of diabetic patients without any subjective symptoms (4). They found seven cases (15.2%) with spontaneous nystagmus and 12 cases (26.1%) with positional nystagmus (4). Almeida in 1998 found over 50% of altered caloric stimulation tests; pendular tracking was the second test with most alterations (21). Rigon *et al*. study in 2007 on the vestibular system in patients with diabetes mellitus type I showed that there are impairment in ENG in 37% of individuals with diabetes mellitus type I (8). Jerger and Jerger showed that 20% of diabetic patients may present dizziness (19). Scherer and Lobo found altered vestibular function in 75% of subjects, with 62.5% presenting no otoneurological complaints (22). Gawron *et al.* (9) noted that vestibular testing appeared to be more sensitive in detecting central nervous system disorders in diabetic patients compared to audiological testing. Metabolic disorders may affect the homeostasis of the vestibular organ more rapidly than the auditory system (13). Presence of conduction anomalies in acoustic pathways of diabetics has also been reported, such as Camisasca found sensorineural hearing loss in 46% of cases, although the degree and configuration were not mentioned in this study (23). Murbach found a negative amplitude variation in the distortion product otoacoustic emissions during hypoglycemia and hyperinsulinemia (24). Mendelson and Roderique showed a reduction in endocochlear potential and cochlear microphonism during the hypoglycemia phase associated to a reduction in potassium concentration and increase in sodium concentration in the endolymph, proving the sensitiveness of the auditory system associated to variations in endolymph composition (25). In a study using auditory brainstem response test to evaluate hearing of children with insulin-dependent diabetes mellitus (IDDM), the authors found elongation of the latency of wave I in 93% of the tested ears and elongation of wave III in 73% of the ears (26). The conduction disturbances in the cochlear nerve (wave I) and brainstem (wave III) were present in normal-hearing children with IDDM (27). Many authors revealed disturbances in neural conduction within the brainstem in patients with type I diabetes even in the case of normal pure tone audiometry (28). There are also reports showing no disturbances in peripheral and central hearing organ in diabetes (26,29). The results obtained show complex pathophysiology of diabetes mellitus as well as individual course of the disease in individual patients.

In the present study there was no statistically significant difference between groups in absolute amplitude and amplitude ratio. In 2008, Bektas *et al.* carried put a study on patients with type II diabetes which showed no difference in absolute amplitude between groups. Perhaps one reason for the lack of significant difference was due to low number of samples in this study. For analysis of brainstem lesions, latencies of VEMP waves are more reliable indicator than the amplitude of VEMP. Therefore prolonged latencies of the VEMP suggest lesions in the retrolabyrinthine, especially in the vestibulospinal tract (16). Since responses were affected in the group with neuropathy more than without neuropathy group, future studies on VEMP responses with more samples in diabetic patients with neuropathy is recommended.

Acknowledgements

The authors are grateful to Mr. Farahani and all members of Department of Audiology (Tehran University of Medical Sciences) for cooperation in this study. Cooperation of Mrs. Afzalzadeh (Diabetes Center, Shariati Hospital, Tehran) and all those who participated in this study is highly appreciated.

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