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ORIGINAL ARTICLE

Video Head Impulse test and Cervical Vestibular Evoked Myogenic Potentials outcomes in Diabetes"

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ABSTRACT

Introduction: Diabetes Mellitus is a worldwide chronic systemic disorder that is characterized by deficiency in insulin secretion from pancreas and/or impairment in its action in its target tissues, which affects daily activities and shortens lifetime, requiring a lifelong management program, resulting in glucose impairments in inner ear leading to vestibular and/or auditory dysfunctions.

Aim: The aim of this study was to assess the impact of type 1 DM and type 2 DM on vestibular system using vHIT and cVEMP.

Methods: This study included 45 patients divided into 3 groups: 15 type 1 DM (Group 1), 15 type 2 DM (Group 2) and 15 apparently healthy age controls (Group 3). **All patients were subjected to:** Full history taking, Otoscopic and basic audiological examination, Vestibular evaluation including: arabic questionnaire version of "Dizziness Handicap Inventory" (DHI), cervical vestibular evoked myogenic potentials and video head impulse test.

Results: Results of this study revealed that there were statistical difference in P13, N23 latencies of cVEMPs, lateral canal gain of vHIT and in lateral canals gain asymmetry. Olso, there were no statistical differences in peak to peak amplitude or asymmetry ratio and in posterior and anterior canals gain, also no significant differences in RALP and LARP gain asymmetry between control and diabetic groups.

Conclusions: Diabetes affects vestibular system at different levels. Type 1 has more prominent effect than type 2. cVEMPs and vHIT has different pathways. Accordingly, they are used as complementary tests in diagnosis of vestibular affection in diabetes.

Key words: DM, cVEMP, vHIT.

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 carbohydrates, fats and protein resulting from abnormalities 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).

Bittar *et al*. reported that glucose metabolism significantly affects 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 (3-4).

It's known that diabetic patients have vestibular dysfunctions which can be evaluated by using VEMP test which is a clinical test of the otolith organs, sensors of linear acceleration. cVEMP was performed as a test of sacculo-collic reflex (5), and vHIT which is a new objective quantitative test of VOR function through measuring the gain of the semicircular canals individually (6).

2. subjects and Methods

"Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans."

2.1. Study design and subjects:

This case-control observational study was carried out in audio-vestibular unit, ENT department, Faculty of Medicine, Zagazig University Hospitals. The sample size was calculated to be 45 divided into 3 groups: 15 type 1 DM (Group 1), 15 type 2 DM (Group 2) and 15 apparently healthy age and sex matched controls (Group 3). All diabetic patients are diagnosed depending on the criteria of The American Diabetes Association (2015), with exclusion criteria of: no history of dizziness or any other systemic diseases (e.g. uncontrolled hypertension, renal failure or hepatic cell failure), cervical lesion with limited neck range of motion, which would prevent subjects from participation in cVEMPs recording**, or** conductive hearing loss that abolishes VEMP.

2.2. Basic audiological assessment:

All patients went through: **Otoscopic examination:** to ensure normal and intact tympanic membrane. **Pure tone audiometry:** Air conduction thresholds were tested at frequencies from 0.25-8KHz and bone conduction thresholds were tested from 0.5-4KHz. **Speech audiometry:** This included speech reception threshold testing (SRT) and word discrimination testing (WD %). **Immittancemetry:** (including both tympanometry and acoustic reflex thresholds) to ensure normal middle ear function.

2.3. The Arabic version of "Dizziness Handicap Inventory":

The DHI is a 25-item self assessment scale to evaluate self-perceived handicap imposed by dizziness. Answers were graded: four for 'yes' response to an item, two for 'sometimes' and zero for 'no'. The DHI is composed of a 9-item functional subscale (36 points), a 9-item emotional subscale (36 points) and a 7-item physical subscale (28 points). Therefore, the scores on the DHI range from 0, denoting no handicap, to 100, indicating significant perceived handicap so that the higher the score, the greater the handicap by dizziness (7).

2.4. Cervical vestibular evoked myogenic potentials:

After appropriate skin cleaning, surface electrodes are 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**.** The patients turn their head by 45º to the contralateral side with slight head flexion by ~30º in the sitting position and the responses were recorded from the ipsilateral SCM muscle (8). The stimulus was delivered monaurally via supra-aural head phone (TDH-39). Stimulus parameters are 500 Hz tone burst stimulus is delivered to the tested ear at an intensity of 100 dB nHL at a rate of 5/s. The analysis time for each response is 50 ms, the number of sweeps are 100 for each run. The response is band-pass filtered between 30 and 1500 Hz (9). Data analysis: Latency of P13, latency of N23 and peak to peak amplitude of P13-N23 complex were measured for all participants in both groups.

The first positive peak occurring around a latency of 13 ms was marked as p1 and the first negative peak following the P13 was marked as n1 (10).

2.5. Video head impulse test:

The vHIT is performed in a seated position in room light. During this procedure, the patient wear a pair of light-weight goggles integrated with a gaze-driven high-speed digital camera system (sampling rate of 220 Hz) that records real time eye movement, a motion sensor that measures head movement and a laser light for calibration. The calibration process is performed via integrated laser dots projected on a wall. After calibration the patient is instructed to fixate on a target located on the wall approximately 1 meter straight ahead (11). At least 10 unpredictable head impulses (amplitude 15º-20º, duration 150-200 ms, target head velocity100-200º/s) are administrated along the planes of the horizontal SCC and in LARP and RALP planes for testing the vertical SCC, respectively (12). The software calculates the vestibulo-ocular reflex gain as the ratio of peak slow phase eye velocity to peak head velocity for each SCC. Refixation saccades are also analyzed and classified as a covert saccade when they occur during head movement and as an overt saccade when they occur after head movement (13).

RESULTS

The results of this study revealed that there were a statistical difference in P13, N23 latencies of cVEMPs, lateral canal gain of vHIT and in lateral canals gain asymmetry. On the other hand, there were no statistical differences in peak to peak amplitude or asymmetry ratio and in posterior and anterior canals gain, also no significant differences in RALP and LARP gain asymmetry between control and diabetic groups.

Table 1: Personal and laboratory characteristics.

Personal characteristics	Control group	Study group		Test value	*P*
		Type 1 DM	**Type 2 DM**		
	n=15	*n*=15	*n*=15		
Age (years) mean±SD	34.9±8.1	37.8±9.9	40.9±8.4	ANOVA F =1.620	0.210
Sex, *n*(%) Males Females	10(67) 5(33)	8(53) 7(47)	7(47) 8(53)	Fisher's Exact value=1.3	0.7
Hb-A1c % mean±SD		6.9±0.12	6.8±0.15	*t*=2.1	0.054
Duration of diabetes (years) mean±SD		15±6.9	13±4.4	6.9	0.35

There were no statistical significant differences in age and sex distribution between control and two study subgroups. The Hb-A1c percentage was higher and the DM duration (years) was longer in type 1 DM, however the difference was not statistically significant between the two study subgroups.

Table 2: Independent samples-t test comparison of the DHI scores in type 1 DM versus type 2 DM

DHI	Type 1 DM n=15	Type 2 DM *n*=15	t	*P*
	mean±SD	**mean±SD**		
Physical	18.4 ±1.5	13.6±2.4	6.5	**<0.001**
Emotional	19.6±1.5	12.8±1.7	11.6	**<0.001**
Functional	20.8±2.1	16.8 ±1.01	6.6	**<0.001**
Total score	58.8±4.7	43.2±3.1	10.8	**<0.001**

Patients with type 1 DM had very high statistically significant different physical, emotional, functional and total DHI score, as compared to type 2 DM.

Table 3: One-way ANOVA comparison of vestibular tests parameters between the control and two study subgroups

Vestibular tests parameters		Control group *n*=15 mean±SD	Type 1 DM *n*=15 mean±SD	Type 2 DM *n*=15 mean±SD	F (*p*) **(ordering)**
P13 latency (ms)	**Right**	13±1.3	18±2.2	16.4±2.1	26.3 **(<0.001)**
	Left	13.6±1	16.6±2.6	16.5±2.2	10.6 **(<0.001)**
N23 latency (ms)	**Right**	22.1±0.78	25±1.5	24±1.8	14.5 **(<0.001)**
	Left	22.3±0.92	24.5±1.7	25±1.9	10.5 **(<0.001)**
Peak to peak amplitude (uV)	**Right**	35.9±7.9	35.8±9.9	31.5±6.8	1.4 (0.26)
	Left	30.3±10.7	35.5±15.1	29.7±10.9	1 (0.38)
Asymmetry ratio (%)		13.9±11.1	11.4±11.3	13.6±8.6	0.48
Lateral canal gain (%)	**Right**	1.06±0.24	0.8±0.21	1.04±0.13	**0.001**
	Left	1.06±0.23	0.87±0.16	1±0.2	**0.035**
Anterior	**Right**	1.08±0.23	1.17±0.20	1.12±0.29	0.57
	Left	1.49 ±0.28	1.52 ±0.3	1.45 ±0.32	0.81
Posterior	**Right**	1.27±0.20	1.34±0.36	1.22±0.22	0.48
	Left	0.94 ±0.1	1.02 ±0.1	1 ±0.29	0.48
Lateral canal gain asymmetry (%)		7.4 ±3.9	15.6 ±4.1	12.4 ±6.5	**<0.001**
RALP		9.4±3.2	13.3±6	12.8±4.5	0.054
LARP		5.8±3	13.8±5.9	13.9±5.5	**<0.001**

There were statistical significant differences in P13 and N23 latencies of right and left ears between control and both study subgroups. On the other hand, there were no statistical significant differences in right and left ears peak to peak amplitude of cVEMPs. There was no statistical

significant difference in asymmetry ratio between the control and two diabetic groups.

There was a statistical significant difference in right and left ears lateral canals gains, but there were no statistical significant differences between anterior and posterior canals gain of the control and diabetic groups. There were very high statistically significant differences in gain asymmetry of lateral and LARP canals, but no statistically significant difference in gain asymmetry of RALP canals in control and diabetic groups.

Table 4: Effect of personal characteristics on vestibular tests parameters in diabetic patients.

Vestibular tests parameters		Age r(p)		gender t(p)		Ear t(p)	
		Type 1 DM	**Type 2 DM**	**Type 1 DM**	**Type 2 DM**	**Type 1 DM**	**Type 2 DM**
DHI total score (%)		0.831	0.573	0.448	0.217		
P13 latency (ms)	**Right**	**0.006**	0.702	0.065	0.062	0.17	0.85
	Left	**<0.000**	0.702	0.188	0.121		
N23 latency (ms)	**Right**	**0.04**	0.457	0.407	0.180	0.78	0.71
	Left	**0.013**	0.934	0.565	0.165		
Peak to peak amplitude (uV)	**Right**	0.061	0.802	0.227	0.151	0.93	0.51
	Left	0.525	0.579	0.509	0.207		
Asymmetry ratio (%)		**0.023**	**0.020**	0.833	0.682		
Lateral canal gain (%)	**Right**	0.105	0.192	0.909	0.188	0.410	0.697
	Left	0.111	0.875	0.592	0.767		
Anterior	**Right**	0.064	0.063	0.424	0.959	0.103	0.084
	Left	0.660	0.937	0.168	0.438		
Posterior	**Right**	0.796	0.632	0.079	0.740	0.145	0.098
	Left	0.946	0.068	0.092	0.311		
Lateral canal gain asymmetry (%)		0.103	0.579	0.942	0.275		
RALP		0.552	0.073	0.210	0.195		
LARP		0.204	0.872	0.789	0.244		

There was a positive correlation between age and total DHI score, but it did not reach significance in both diabetic groups. Gender revealed non-significant effect on DHI total score.

In type 1 and 2 DM, there was a statistically significant positive correlation between age and *cVEMPs' latencies* and *asymmetry ratio*. The amplitude showed negative correlation with age but did not reach significance. There was no statistically significant effect of gender and ear effect on any of the cVEMPs parameters in both diabetic groups.

There were no statistically significant effect of age, gender and ears effect on any of the vHIT parameters in both diabetic groups.

Table 5: Effect of diabetic characteristics on vestibular tests parameters in diabetic patients.

Vestibular tests parameters		Hb-A1c r(p)		DM duration r(p)	
		Type 1 DM	**Type 2 DM**	**Type 1 DM**	**Type 2 DM**
DHI total score (%)		0.321	0.647	**0.038**	**0.003**
P13 latency (ms)	**Right**	**0.001**	**0.003**	**0.045**	0.202
	Left	**0.004**	**0.003**	**0.029**	0.327
N23 latency (ms)	**Right**	0.57	0.121	0.131	0.243
	Left	0.34	**0.034**	0.673	0.813
Peak to peak amplitude (uV)	**Right**	**<0.001**	**0.001**	0.24	0.465
	Left	**0.04**	**<0.001**	0.241	0.132
Asymmetry ratio (%)		0.129	0.071	0.101	0.071
Lateral canal gain (%)	**Right**	**0.010**	0.416	**0.019**	0.069
	Left	**0.002**	0.300	**0.043**	0.75
Anterior	**Right**	0.410	0.332	**0.005**	0.540
	Left	0.849	0.620	**0.034**	0.109
Posterior	**Right**	0.180	0.792	0.079	0.770
	Left	0.250	0.46	**0.004**	0.510
Lateral canal gain asymmetry (%)		**0.030**	**0.016**	**0.031**	**0.015**
RALP		**<0.001**	0.85	**0.029**	0.060
LARP		0.035	**0.01**	0.021	0.02

There was a positive correlation between Hb-A1c and the total DHI score that was not significant. Regarding the *DM duration*, it showed a high statistically significant strong positive correlation with the total DHI score in both groups.

In both types of DM, the Hb-A1c showed statistically significant positive correlation with *P13 latency* and a statistically significant negative correlation with *peak to peak amplitude* in both ears. The N23 latency had a positive correlation with HbA1C but did not reach significance except in left ear of patients with type 2 DM. The asymmetry ratio had a positive correlation with HbA1C but was not significant in both diabetic groups. There was positive correlation between DM duration and P13 and N23 latencies in both diabetic groups but only was statistically significant there were negative correlation between Hb-A1c and vHIT gain of all canals in both ears that were not significant Also, the negative correlation of peak to peak amplitude were not significant.

In type 1 DM, there were statistically significant negative correlations between Hb-A1c and vHIT gains in both ears that were significant in *lateral canals* only in type 1 DM and in all canals in type 2 DM that were not significant . In addition, there were positive correlation between Hb-A1c and gain asymmetry that were significant at *lateral and RALP canals* in type 1 DM and at *lateral and LARP canals* in type 2 DM.

4. DISCUSSION

The study involved two groups of both gender and ranging in age from 20 to 50

years: the control group included 15 healthy adults and the study group included 30 patients with DM who were classified into two subgroups; type 1 DM and type 2 DM. Each subgroup included 15 patients matched with control group in age and gender. The study design enrolled the diabetic patients based on the criteria of the **American Diabetes Association**. The Hb-A1c percentage and DM duration (years) were greater in type 1 DM; however the difference was not significant between the diabetic groups. Numerous subjective factors that could alter or interfere with the cVEMPs and vHIT recording were excluded (table 1).

Findings of Dizziness Handicap Inventory:

The DHI was studied in both diabetic groups (table 2) and showed significantly higher physical, emotional and functional disabilities as well as higher total DHI score in type 1 DM. This was in concordant with the results of **Biurrun et al.** (14). They found that longer duration of metabolic changes in type 1DM was accompanied by neuropathy and angiopathy that causes vestibular dysfunction. These finding suggest that the chronic hyperglycemia of diabetes in type 1 is probably associated with long term damage. The range of vestibular organ impairment in type 1 DM seems to depend mainly on the presence and character of hypoglycemic incidents and the duration of the disease, where the type 1 DM starts at younger age hence has longer duration than type 2 DM (15-16).

Findings of Cervical Vestibular Evoked Myogenic Potentials:

In the current study, results of cVEMPs testing showed statistical significant delay in P13 and N23 latencies in both ears of diabetic patients than the control group(table 3), which indicates sacculo-colic reflex pathway lesion. On further analysis of the results, no significant difference was found between type 1 and type 2 DM.

Consistent to the current findings, **Ward et al.** (17) indicated delayed cVEMPs latencies in approximately 50% of diabetic patients. Similarly, **Kamali et al.** (16) observed delayed cVEMPs latencies in type1 diabetics who had peripheral neuropathy. They suggested that the cVEMPs may additionally be affected in participants with longer disease durations and poorer disease control. They suggested that the delayed cVEMPs may be indicative of neuropathy similar to the neurovascular damage seen in diabetics with peripheral neuropathy in patients with DM, where prolonged latencies in nerve conduction studies are considered diagnostic (18).

On the other hand, in this study there was no statistically significant difference of peak to peak amplitude of cVEMPs bilaterally between control and diabetic groups (table 3). This finding was consistent with that of **Kamali et al.** (16) who reported that peak latencies of cVEMPs is more sensitive in detecting vestibular affection in diabetic patients than peak amplitudes.

In this study, there was no statistical significant difference in asymmetry ratio between control and diabetic groups (table 3). This was in agreement with **Minnaar et al.** (19) and **Konukseven et al.** (20). It was reported that bilateral neural dysfunction was recognized in cVEMPs findings and lateralization was not seen in cVEMPs asymmetric ratios (20). Moreover, the diagnostic value of amplitude asymmetry measurements in diabetics is low because of the large overlap of the cVEMPs amplitude asymmetry range for vestibular lesions with that of normal subjects (21).

Findings of Video Head Impulse test:

In this study, the lateral canal gain in both ears showed a highly statistical significance difference between diabetics and control groups. On the other hand, there was no statistical significant difference between the groups' gain of anterior and posterior canals (table 3). Further analysis was done to compare between the control and two study subgroups regarding lateral gain. In both ears, the test revealed that lateral gain decreased in type 1 and type 2 DM patients compared to control group, with type 1 DM having the lowest gain (table 3). This finding is indicative of the poorest right lateral canal function in the type 1 DM.

Moreover, the current study agreed with **Minnaar et al.** (19) in the poorer lateral canal but in right ear only; the right side appeared to be more prone to impaired functioning as reflected by both the results of the pure tone testing and the vHIT.

As regards Gain asymmetry, there were very high statistical significant differences in gain asymmetry of lateral and LARP positions, but no statistically significant differences in gain asymmetry of RALP position in control and study groups. Further analysis was done using Tukey's post hoc test that revealed increased lateral and LARP gain asymmetry in type 1 and type 2 DM patients compared to controls. However, there was no significant difference between two types of diabetes.

The difference in affection between semicircular canals may be due to their different anatomical positions, metabolic and vascular characteristics (17). Consequently, the magnitude of the five vestibular organs decline was asymmetric throughout the vestibular apparatus and that not all of the vestibular end organs were equally affected (22).

Variables effect on vestibular tests outcome in diabetic patients

Variables effect on Dizziness Handicap Inventory:

This study revealed poorer DHI score with age increase; however this change was not significant (table 4). A study conducted by **Agrawal et al.** (22) supported the current finding. They demonstrated a global decline in vestibular function associated with aging. The non-significant effect of age in this study could be related to the young and middle age of the subjects involved; whereas the age of starting to decline in vestibular functions was reported to start as early as 40 years (23).

On the other hand, there was a statistically significant strong positive correlation between DM duration and DHI total score. This is matched with the notion that vestibular functions could be affected in participants with longer disease durations, which consequently affect patient's life styles (16).

Variables effect on Cervical Vestibular Evoked Myogenic Potentials:

The present study revealed significant positive effect of age on cVEMPs' latencies and asymmetry ratio in type 1 DM and only on the asymmetry ratio in type 2 DM (table 4). As type 1 starts at younger age, thus the vestibular system is more exposed to the metabolic disturbances than in a comparable age group of type 2 DM. This causes more degeneration of type 1vestibular hair cells in type 1 diabetic patients. Histopathological evidence also reports greater degrees of age-related hair cell loss and degradation of the otoconia in the saccule (24).

Regarding diabetes duration, there was a statistical significant positive correlation between DM duration and P13 latency in both ears of type 1 DM (table 4). Prolonged duration of DM causes degradation of the otoconia in the saccule (24). The effect of diabetic characteristics on cVEMPs measures confirms the importance of cVEMPs in monitoring saccular dysfunction in diabetic patients in addition to other vestibular testing (table 5).

Variables effect on Video Head Impulse test:

Findings of this study revealed that the gain of vHIT was reduced and gain asymmetry was increased with age increase in both diabetic groups; however the effect of age was not significant (table 4).Regarding the individual function of the vestibular end organs, research has revealed that the functions of all six semicircular canals decline with age starting at age of 40 years (25). Therefore, the age effect in the present study did not reach significance. A study by **Agrawal et al.** (22) also indicated a significant decline with the aging process in the function of each individual semicircular canal. Moreover, symmetrical vHIT measures were obtained from both genders and both ears in both diabetic groups (table 4). This indicates that the vestibular insults in DM affect both ears equally.

There were statistically significant negative correlations between Hb-A1c and vHIT gains in both ears of both diabetic groups that were significant in lateral canals

of type 1 DM (table 5). Furthermore, there was a positive correlation between Hb-A1c and vHIT gain asymmetry in both ears of both diabetic groups that were significant in lateral and RALP canals of type 1 DM and in lateral and LARP canals in type 2 DM. More involvement of vHIT measures in type 1 DM is indicative of the severity of vestibular involvement in this group. Diabetes duration showed negative correlations with the gain measure and positive correlations with gain asymmetry measure in both ears of both diabetic groups. A significant effect was found mainly in type 1DM (table 5).

The higher prevalence of vestibular dysfunction in DM was specifically seen in people with longer duration of diabetes and higher Hb-A1c. This caused by the numerous microvascular complications that are associated with diabetes and the toxic effect of long-term hyperglycemia. **5. Conclusions:**

Diabetes Mellitus affects vestibular system at different levels and type 1 has more effect than type 2 due to its long term pathology. For assessment of sacculo-collic reflex lesions in diabetics, latencies of cVEMPs waves are more reliable indicator than the amplitude measure. Video HIT is the only test that assesses all six semicircular canals independently and with a physiological stimulus, similar to how the patient uses the VOR system in daily life. The HBAIC % and duration of diabetic pathology are the most prominent factors correlated with severity of vestibular dysfunction in diabetic patients. Each of the cVEMPs and vHIT has different pathway. Accordingly, they could be used as complementary tests in diagnosis of vestibular affection in diabetic patients.

6. RECOMMENDATIONS

Efforts should be directed to increase awareness of vestibular disorders in DM. Routine assessment of vestibular function in diabetic patients is recommended for early diagnosis and management planning to avoid its impact on the quality of life. The vHIT and cVEMP could be used as complementary tests to provide a comprehensive evaluation of the vestibular system in diabetics. This combination could be applied to assess vestibular functions in population who are highly vulnerable to vestibular dysfunction e.g. hypertension and metabolic disorders.

Conflict of interest: no

Financial disclosure : no

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