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Editorial Board Member of *World Journal of Clinical Pediatrics*, Khaled Saad, MD, PhD, Professor, Department of Pediatrics, University of Assiut, Asyut, 71516, Egypt. khaled.ali@med.au.edu.eg

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Case Control Study

Vestibular function for children with insulin dependent diabetes using cervical vestibular evoked myogenic potentials testing

Sherifa Ahmed Hamed, Kotb Abbas Metwalley, Hekma Saad Farghaly, Amira Mohamed Oseily

ORCID number: Sherifa Ahmed Hamed 0000-0002-1441-3530; Kotb Abbas Metwalley 0000-0003-4763-488X; Hekma Saad Farghaly 0000-0002-1904-7170; Amira Mohamed Oseily 0000-0001-6892-8364.

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Sherifa Ahmed Hamed, Department of Neurology and Psychiatry, Assiut University Hospitals, Assiut 71516, Egypt

Kotb Abbas Metwalley, Hekma Saad Farghaly, Department of Pediatrics, Assiut University Hospitals, Assiut 71516, Egypt

Amira Mohamed Oseily, Department of ENT (Auditory Unit), Assiut University Hospitals, Assiut 71516, Egypt

Corresponding author: Sherifa Ahmed Hamed, MD, Professor, Department of Neurology and Psychiatry, Assiut University Hospital, Floor # 7, Room # 4, P.O.Box, Assiut 71516, Egypt. hamedsherifa@aun.edu.eg

Abstract

BACKGROUND

Healthy vestibular system adjusts balance during static and dynamic conditions. This is important for normal development (standing up and walking). Vestibulopathies (central and peripheral) are common complications of diabetes in adult population. Related studies are scarce in children with type 1 diabetes (T1D).

AIM

To assess saccular function of otolith organ in children with T1D and predictors for its dysfunction.

METHODS

Cervical vestibular evoked myogenic potential (cVEMP) was used for objective evaluation.

RESULTS

The study included 40 patients (boys = 15; girls = 25). Patients had mean age of 13.63 ± 1.50 years, duration of diabetes of 5.62 ± 2.80 years, frequent attacks of diabetic ketoacidosis (55%) and hypoglycemia (30%), hyperlipidemia (20%), hypertension (12.5%) and peripheral neuropathy (40%). Dizziness was found in 10%. Compared to healthy children ($n = 25$), patients had prolonged cVEMP P1 and N1 latencies and reduced P1-N1 amplitude. Bilateral cVEMP abnormalities were found in 60% (*vs* 25% for unilateral abnormalities). Higher frequencies and severe vestibulopathies were found with chronic diabetes of > 5 years, hemoglobin A1c values $> 7\%$, frequent diabetic ketoacidosis and hypoglycemic

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attacks and presence of dizziness. Regression analyses showed that predictors for prolonged P1 latencies and reduced P1-N1 amplitudes were only chronic diabetes (> 5 years) {odds ratio (OR) = 2.80 [95% confidence interval (CI): 1.80–5.33], $P = 0.01$; OR = 3.42 (95%CI: 2.82–6.81)} and its severity (hemoglobin A1c > 7%) [OR = 3.05 (95%CI: 2.55–6.82), $P = 0.01$; OR = 4.20 (95%CI: 3.55–8.50), $P = 0.001$].

CONCLUSION

Dysfunction or injury of the saccular macula and its pathways is prevalent in children with T1D. Optimum glycemic control is important to prevent diabetes related vestibulopathies.

Key Words: Children; Type 1 diabetes; Otolith organ; Cervical vestibular evoked myogenic potential

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Core Tip: Vestibulopathies are common complications of diabetes. The vestibular system is crucial for early normal motor and mental developments. Vestibular evoked myogenic potential testing is objective, noninvasive, inexpensive, rapid and reliable. It is used to assess the function of otolith organs (sacculae and utricle) of the inner ear. The otolith organs register forces related to linear acceleration and static tilt to the gravitational axis. Cervical vestibular evoked myogenic potential is vestibulo-colic reflex record from neck muscles in response to acoustic stimulation. It provides information about type 1 hair cells in saccular macula, inferior vestibular nerve, vestibular nuclei, lateral and medial vestibulospinal tracts and accessory nerve nuclei. This study aimed to evaluate saccular function in children with type 1 diabetes and predictors of its abnormalities.

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INTRODUCTION

Large epidemiological studies in the United States have shown an increase in the prevalence of type 1 diabetes (T1D) from 1.48/1000 to 1.93/1000 between years of 2001 and 2009. They also have shown an increase in the annual incidence of T1D in children and adolescents by 1.4% during the years 2002 to 2012[1]. In Egypt, the annual incidence of T1D in younger children (age: Below 15 years) has been estimated to be 8/100000[2]. Previous studies reported that diabetes mellitus (DM) is the cause of peripheral and central auditory and vestibular systems' dysfunctions (*i.e.* vestibulopathies)[3-9]. Vestibular system is important for healthy motor (standing up and walking) development. It adjusts balance during static condition and motion. The vestibular end organs and their connections maintain gaze and postural stabilities through the vestibulo-ocular and vestibulo-spinal reflexes[10,11]. Studies found significant associations between diabetes and manifestations of vestibular dysfunction (*e.g.*, imbalance, unsteadiness, vertigo, *etc.*) independent to other diabetic complications that cause balance disturbance, including proprioception impairment with diabetic neuropathy and defective vision with diabetic retinopathy[10,12]. Functional testing of vestibular system are (1) Caloric irrigation, rotatory chair testing, head-impulse test (HIT) and electronystagmography (ENG) or videonystagmography (VNG), tests for semicircular canals or horizontal angular head acceleration (vestibulo-ocular) and superior vestibular nerve functions; and (2) Vestibular evoked myogenic potentials (VEMPs), tests for otolith organs' (sacculae and utricle) functions[13]. The otolith organs register forces related to linear acceleration and static tilt with gravity [11,13]. VEMP testing is objective, noninvasive, inexpensive, rapid and reliable. It causes no discomfort to subjects compared to ENG or VNG. There are two common

types of VEMP recording: (1) Ocular or oVEMP: It is used to assess the integrity of the utricle or a superior vestibular nerve function; and (2) Cervical or cervical VEMP (cVEMP): It is used to assess the integrity of saccular macula or an inferior vestibular nerve function. cVEMP is a short-latency vestibulo-collic reflex (VCR) recorded from neck muscles in response to acoustic stimulation. The otolith organs sense intense acoustic stimulation due to its anatomical proximity to the cochlea[13]. The VCR arc is composed of: (1) Receptors, which are type 1 vestibular hair cells of saccular macula; (2) Afferent pathway, which is the inferior vestibular nerve that relays in the vestibular nuclei; and (3) Efferent fibers of vestibular nuclei, which run along the lateral and medial vestibulo-spinal tracts to the accessory nerve nucleus to supply the sternocleidomastoid muscle (SCM)[14].

Objectives

Studies of vestibular function in children with T1D are lacking. We aimed to assess saccule and its connections' functions using cVEMP testing. The predictors (demographic, clinical and laboratory variables) of vestibular dysfunctions were also determined.

MATERIALS AND METHODS

Study design, period, region

This is a cross sectional case-control study. It included 40 children with T1D (boys = 10, 25%; girls = 30, 75%) and 25 healthy children (boys = 9, 36%; girls = 16, 64%; age range: 9-18 years; mean: 15.44 ± 1.22 years). Children with diabetes were recruited over a year (December 2019–November 2020) from the Endocrinology Clinic of Children's Hospital, Assiut University, Assiut, Egypt. Healthy children were patients' friends and schoolmates. Excluded were children with: (1) External or middle ear diseases; (2) History of head or neck injuries or limitation of neck movements; (3) History of otologic surgery; (4) Regular or recent intake of ototoxic drugs; and (5) History of primary neurologic, psychiatric or other medical disease.

The protocol of work was approved by the research ethics committee of Faculty of Medicine, Assiut University, Assiut, Egypt, No. AUFM_PED_232/2019. Informed written consent to participate in the study was obtained from children's parents or guardians.

Methods

Clinical evaluation: Detailed ear, nose and throat, physical and neurological data were gathered. Data included age at onset and duration of diabetes, family history of diabetes and insulin dose. They also included history of diabetic complications [whether due to the disease or its medications: *e.g.*, diabetic ketoacidosis (DKA), retinopathy, nephropathy, peripheral neuropathy, hypoglycemia, *etc.*], comorbid medical conditions (*e.g.*, other endocrinal disease, hypertension, hyperlipidemia, *etc.*) and hearing or vestibular symptoms. All underwent medical, neurological and ear, nose and throat examinations. The presence of peripheral neuropathy was diagnosed by clinical manifestations and abnormal nerve conduction velocity study in at least two nerves; one must have been the sural nerve.

Audiologic assessment: It included otoscopic ear examination; screening audiograms (250–4000 Hz), tympanometry (200 top–400 dapa) and acoustic (stapedius) reflex (Middle Ear Analyzer Interacoustics, Az26, Assens, Denmark). Speech discrimination thresholds were assessed by identifying the hearing level for understanding and repeating a set of 10 monosyllables. Typically, normal Speech Discrimination Score ranges from 90% to 100%.

Vestibular assessment: It was done by recording cVEMP response from each ear (GN Otometrics, Schaumburg, IL, United States). The stimulus was air-conducted tone burst at frequency of 500 Hz, intensity of 100 dBnHL and rate of 5.1/s. Responses to 200 stimuli were averaged and band-pass filtered between 30-300 Hz for each repetition. The child lay supine and was instructed to turn the head to contralateral side and look at a fixed target on the examination room's wall and right after towards a fixed point located above this target, to induce a vertical viewing angle of approximately 30° above the horizontal plane. The impedance values for the device were checked before each recording to be < 5 KOhms. Four surface electrodes were applied: (1) An active electrode, placed on the middle of ipsilateral SCM; (2) A reference

electrode, placed on ipsilateral mastoid; (3) A ground electrode, placed on the forehead; and (4) A fourth electrode, placed on the contralateral mastoid. Data acquisition was accepted by the device if SCM electromyography (EMG) activity was 50-100 μ V. Rectified EMGs from 20 milliseconds (ms) before to 80 ms afterwards were collected. To control for the individual differences of SCM contractions during recording, the raw amplitude of each recording was divided over the mean rectified EMG activities, which were recorded for 10 ms before the stimulus onset. VEMP parameters were: (1) Latencies of P1 (P13) and N1 (N23) waves; (2) P1-N1 peak-to-peak amplitude; and (3) Amplitude asymmetry ratio (AR), an inter-aural amplitude difference. AR suggests the side of pathology in unilateral lesions or the severely injured side in bilateral lesions. AR is calculated as follows: $AR\% = (AL - AR)/(AL + AR) \times 100$, where AL and AR are the amplitudes due to stimulation of the left and right ears. A clinically significant AR% is $> 35\%$ [15]. The absence of defined P1 and N1 waves indicate absent cVEMP response.

Statistical analysis

SPSS, version 22.0 (SPSS Inc., Armonk, NY, United States) was used for statistical analyses. Normality of data was checked by Kolmogorov-Smirnov test. Descriptive statistics were expressed as means \pm SD or medians (25th, 50th, 75th percentiles). Differences between groups were calculated by inference statistics (Chi-square with Fisher's exact tests or Mann-Whitney *U* test). Abnormal P1 or N1 latencies were considered if exceeded at least two standard deviations of the mean value for controls. Abnormal P1-N1 amplitude was considered if was less than the 5th percentile of the mean value for controls. Correlations between cVEMP and subjects' variables were done using Spearman's correlation coefficient. The independent associations between vestibular and subjects' variables were determined using multiple logistic regression analysis by calculating the odds ratio (OR) and 95% confidence interval (95% CI). For 2-sided statistics, significant values were considered with probability value less than 0.05.

RESULTS

In this study, 130 ears were examined (patients = 80; controls = 50). Children with T1D had mean age of 13.63 ± 1.50 years and duration of illness of 5.62 ± 2.80 years. Frequent DKA and hypoglycemic attacks were found in 55% and 30%, respectively. The reported comorbid medical conditions and diabetic complications were hyperlipidemia (20%), hypertension (12.5%) and sensory peripheral neuropathy (40%). Manifestations of peripheral neuropathy were lower limbs' numbness, stoking hypoesthesia and reduced sensory unit potential's amplitudes of sural nerves without (axonal neuropathy) or with prolonged distal latencies or reduced nerve conduction velocities (demyelinating neuropathy) (Table 1). Both children with diabetes and healthy children had normal otoscopic ear examination, acoustic reflexes, pure tone audiogram and Speech Discrimination Scores (right ear: 96.32 ± 2.50 ; left ear = 93.44 ± 2.28) and type A tympanometry. Dizziness, not related to hypoglycemia, was reported in 10% ($n = 6$).

Compared to healthy children, patients had significant prolongation in cVEMP P1 and N1 latencies and reduction in P1-N1 amplitudes (Table 2). Bilateral cVEMP abnormalities were found in 25% (for latencies) and 60% (for amplitude), respectively. AR was found in 25%. No sex difference was found in cVEMP changes. Children with chronic diabetes with duration > 5 years had prolonged P1 and N1 ($P = 0.006$; $P = 0.01$) latencies and reduced P1-N1 amplitudes ($P = 0.001$) compared to those with short diabetes duration (≤ 5 years). Children with dizziness had prolonged P1 and N1 ($P = 0.02$; $P = 0.02$) latencies and reduced P1-N1 amplitudes ($P = 0.01$) compared to those without dizziness. Children with high hemoglobin A1c (HbA1c)% values ($> 7\%$) had prolonged P1 and N1 ($P = 0.01$; $P = 0.01$) latencies and reduced P1-N1 amplitudes ($P = 0.001$) compared to those with HbA1c% values $\leq 7\%$. Children with history of DKA attacks had prolonged P1 and N1 ($P = 0.003$; $P = 0.001$) latencies and reduced P1-N1 amplitudes ($P = 0.01$) compared to those without. Children with hypoglycemic attacks had prolonged P1 and N1 ($P = 0.02$; $P = 0.03$) latencies and reduced P1-N1 amplitudes ($P = 0.03$) compared to those without. Children with peripheral neuropathy had prolonged P1 and N1 ($P = 0.001$; $P = 0.03$) latencies and reduced P1-N1 amplitudes ($P = 0.02$) compared to those without (Table 3). Significant correlations were identified between P1 with N1 latencies ($r = 0.335$, $P = 0.01$) but not between P1 with P1-N1

Table 1 The demographic, clinical and laboratory characteristics of the studied children

| Demographic, clinical and laboratory characteristics | Patients (n = 40) | Controls (n = 25) | P value |
|--|----------------------------|----------------------------|---------|
| Age, yr | 10-18 (13.63 ± 1.50) | 9-18 (15.44 ± 1.22) | 0.438 |
| Sex, n (%) | | | |
| Male | 10 (25) | 9 (36) | 0.185 |
| Female | 30 (75) | 16 (64) | 0.223 |
| BMI | 15.70-25.30 (20.53 ± 2.52) | 15.20-27.50 (18.86 ± 2.63) | 0.278 |
| Systolic blood pressure, mmHg | 100-130 (110.80 ± 10.50) | 100-120 (105.00 ± 8.50) | 0.365 |
| Diastolic blood pressure, mmHg | 60-80 (70.55 ± 2.34) | 60-70 (68.33 ± 5.20) | 0.544 |
| Age at onset of diabetes, yr | 4-15 (8.54 ± 2.33) | - | - |
| Duration of diabetes, yr | 3-10 (5.62 ± 2.80) | - | - |
| ≤ 5 | 9 (22.5) | | |
| > 5 | 31 (77.5) | | |
| DKA, n (%) | 22 (55) | - | - |
| Number of attacks | 0-6 (3.44 ± 0.43) | | |
| Hypoglycemia, n (%) | 12 (30) | - | - |
| Number of attacks | 0-6 (2.50 ± 0.32) | | |
| Family history of diabetes, n (%) | 18 (45) | 3 (12) | 0.01 |
| Hb1Ac, n (%) | 5.00-15.65 (8.68 ± 1.50) | 3.00-6.00 (3.90 ± 0.25) | 0.001 |
| ≤ 7% | 4 (10) | | |
| > 7% | 36 (90) | | |
| Insulin dose, IU/kg/d | 0.80-2.10 (1.70 ± 0.32) | - | - |
| Lipid profile, mg/dL | | | |
| Total cholesterol | 100-250 (180.20 ± 20.50) | 90-200 (140.21 ± 15.65) | 0.06 |
| Triglycerides | 60-280 (168.52 ± 22.50) | 50-120 (80.50 ± 20.58) | 0.001 |
| LDL | 50-160 (100.65 ± 10.62) | 65-110 (85.43 ± 6.46) | 0.08 |
| HDL | 45-65 (55.52 ± 5.33) | 35-70 (48.33 ± 5.62) | 0.364 |
| Comorbid medical conditions, n (%) | | | |
| Hypertension | 5 (12.5) | - | - |
| Hypercholesterolemia/ dyslipidemia | 8 (20) | - | - |
| Serum creatinine, mg/dL | 0.54-1.20 (0.80 ± 0.15) | 0.40-0.90 (0.62 ± 0.05) | 0.450 |
| Diabetic complications, n (%) | | | |
| Nephropathy | 6 (15) | - | - |
| Peripheral neuropathy | 16 (40) | - | - |
| Dizziness, n (%) | 6 (10) | - | - |

BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; Hb1Ac: Hemoglobin A1c; DKA: Diabetic ketoacidosis.

amplitudes ($r = 0.230$, $P = 0.185$). Multiple regression analysis showed that presence of prolonged P1 latencies and reduced P1-N1 amplitudes were significantly correlated with longer diabetes duration (> 5 years) [OR = 2.80 (95%CI: 1.80-5.33), $P = 0.01$; OR = 3.42 (95%CI: 2.82-6.81)] and higher HbA1c levels (> 7%) [OR = 3.05 (95%CI: 2.55-6.82), $P = 0.01$; OR = 4.20 (95%CI: 3.55-8.50), $P = 0.001$] but not with the presence of complications or comorbid medical conditions or dizziness.

Table 2 Cervical vestibular evoked myogenic potential results of the studied groups (mean ± SD)

| Variables | Children with T1D (n = 40) | Controls (n = 25) | P value (P1) | P value (P2) |
|-------------------------------------|----------------------------|----------------------------|--------------|--------------|
| P1 latency, n ¹ (%) | | | | |
| Unilateral | 6 (15) | - | - | - |
| Bilateral | 10 (25) | - | - | - |
| Range, ms | | | | |
| Right ear | 18.00–22.00 (20.16 ± 1.34) | 10.40–16.40 (12.03 ± 1.01) | 0.03 | 0.542 |
| Left ear | 13.00–29.00 (20.40 ± 1.10) | 10.40–17.60 (14.25 ± 1.68) | 0.02 | |
| N1 latency, n ¹ (%) | | | | |
| Unilateral | 6 (15) | - | - | - |
| Bilateral | 10 (25) | - | - | - |
| Range, ms | | | | |
| Right ear | 22.00–33.00 (28.30 ± 2.66) | 18.65–26.70 (22.43 ± 1.82) | 0.04 | 0.364 |
| Left ear | 24.00–36.80 (32.35 ± 2.84) | 16.82–30.82 (26.45 ± 1.02) | 0.03 | |
| P1-N1 amplitude, n ¹ (%) | | | | |
| Unilateral | 10 (25) | - | - | - |
| Bilateral | 24 (60) | - | - | - |
| Range, μV | | | | |
| Right ear | | | | |
| Range | 20.00–90.00 | 48.60–92.80 | 0.001 | 0.458 |
| Median | 44.20 | 72.43 | | |
| 25 th | 36.00 | 60.35 | | |
| 50 th | 40.45 | 76.44 | | |
| 75 th | 48.55 | 86.62 | | |
| Left ear | | | | |
| Range | 26.68–86.00 | 46.03–98.00 | 0.001 | |
| Median | 46.20 | 74.68 | | |
| 25 th | 33.25 | 54.36 | | |
| 50 th | 45.00 | 80.00 | | |
| 75 th | 56.25 | 88.56 | | |
| AR | | | | |
| Range | 1.12–66.20 | 0.0–15.8 | 0.001 | |
| Median | 18.30 | 4.88 | | |
| 25 th | 6.58 | 1.88 | | |
| 50 th | 13.36 | 2.90 | | |
| 75 th | 32.44 | 6.30 | | |
| n ¹ (%) | 10 (25) | 0 | | |

¹Number of subjects with vestibular evoked myogenic potential abnormalities results.

P1: Significance for patients *vs* controls; P2: Significance for patients' right *vs* left ear; AR: Asymmetry ratio; T1D: Type 1 diabetes.

DISCUSSION

Developments in research have shown that vestibulopathies are common complications of DM[7-9]. The results of this study showed that: (1) The majority (75%) of children with T1D had asymptomatic vestibular dysfunctions. Few had dizziness

Table 3 Cervical vestibular evoked myogenic potential's results for children with type 1 diabetes in relation to their demographic, clinical and laboratory variables

| Variables | P1 | N1 | P1-N1 amplitude | AR |
|---------------------------------|---------------|---------------|-----------------|--------|
| Sex | | | | |
| Male (n = 10) | 22.35 ± 1.12 | 26.32 ± 2.30 | 44.82 | 10.33 |
| P1 | 0.02 | 0.320 | 0.01 | 0.01 |
| Female (n = 30) | 18.22 ± 1.63 | 32.55 ± 1.22 | 38.36 | 16.85 |
| P1 | 0.04 | 0.01 | 0.001 | 0.001 |
| P2 | 0.125 | 0.01 | 0.06 | 0.126 |
| Duration of diabetes, yr | | | | |
| ≤ 5 yr (n = 9) | 16.68 ± 1.23 | 22.65 ± 2.22 | 38.30 | 6.50 |
| P1 | 0.02 | 0.244 | 0.03 | 0.05 |
| > 5 yr (n = 31) | 28.33 ± 1.11 | 35.07 ± 2.31 | 56.26 | 18.68 |
| P1 | 0.01 | 0.01 | 0.001 | 0.0001 |
| P2 | 0.006 | 0.01 | 0.001 | 0.452 |
| Dizziness | | | | |
| Yes (n = 6) | 26.03 ± 1.33 | 34.68 ± 2.57 | 38.64 | 10.64 |
| P1 | 0.002 | 0.01 | 0.001 | 0.01 |
| No (n = 32) | 16.23 ± 1.28 | 28.05 ± 2.28 | 56.00 | 16.28 |
| P1 | 0.138 | 0.302 | 0.001 | 0.001 |
| P2 | 0.02 | 0.03 | 0.01 | 0.06 |
| Hb1Ac, % | | | | |
| ≤ 7 (n = 4) | 16.83 ± 1.30 | 22.01 ± 1.20 | 60.00 | 8.64 |
| P1 | 0.306 | 0.358 | 0.08 | 0.023 |
| > 7 (n = 36) | 25.633 ± 1.28 | 34.55 ± 1.33 | 32.50 | 18.28 |
| P1 | 0.04 | 0.01 | 0.001 | 0.804 |
| P2 | 0.01 | 0.01 | 0.001 | 0.246 |
| DKA | | | | |
| Yes (n = 22) | 27.23 ± 1.20 | 34.25 ± 1.88 | 38.50 | 16.35 |
| P1 | 0.01 | 0.01 | 0.001 | 0.001 |
| No (n = 18) | 14.84 ± 1.11 | 21.15 ± 1.23 | 55.84 | 8.00 |
| P1 | 0.358 | 0.682 | 0.01 | 0.04 |
| P2 | 0.003 | 0.001 | 0.01 | 0.323 |
| Hypoglycemia | | | | |
| Yes (n = 12) | 26.86 ± 1.80 | 34.22 ± 2.02 | 30.40 | 12.86 |
| P1 | 0.01 | 0.01 | 0.001 | 0.01 |
| No (n = 28) | 16.50 ± 1.44 | 25.24 ± 2.562 | 54.68 | 10.35 |
| P1 | 0.05 | 0.05 | 0.01 | 0.01 |
| P2 | 0.02 | 0.03 | 0.03 | 0.286 |
| Peripheral neuropathy | | | | |
| Yes (n = 16) | 23.28 ± 1.30 | 32.26 ± 1.45 | 35.06 | 16.60 |
| P1 | 0.001 | 0.01 | 0.001 | 0.01 |
| No (n = 24) | 16.44 ± 1.03 | 24.24 ± 1.40 | 52.66 | 13.44 |

| | | | | |
|------------------|--------------|--------------|-------|-------|
| P1 | 0.458 | 0.542 | 0.01 | 0.01 |
| P2 | 0.02 | 0.03 | 0.02 | 0.322 |
| Control subjects | 13.22 ± 1.30 | 23.82 ± 1.37 | 74.68 | 4.88 |

DKA: Diabetic ketoacidosis; P1: Significance *vs* controls; P2: Significance for a *vs* b for each variable.

(10%); (2) Bilateral vestibular dysfunction was more frequent than unilateral (25%-60% *vs* 10%-25%); and (3) Chronicity and severity of diabetes are the predictors for its related vestibulopathies.

The authors in this study found reduced P1-N1 amplitudes in 85% of children with T1D, and 40% had prolonged P1 and N1 latencies. Previous studies reported similar findings. Kamali *et al*[7] found prolonged P13 and N23 latencies ($P < 0.05$) but normal absolute and relative P1-N1 amplitudes of cVEMP in patients with T1D ($n = 10$) with an age range from 15 to 40 years compared to matched healthy subjects ($n = 24$). Their patients did not have diabetic neuropathy. Konukseven *et al*[8] found prolonged oVEMP and cVEMP latencies in patients with diabetes ($n = 30$) compared to prediabetes ($n = 30$) and healthy controls ($n = 31$). They did not find differences in VEMP amplitudes among the three groups. Kalkan *et al*[9] found reduced cVEMP and oVEMP amplitudes in patients with diabetes whether they had ($n = 33$) or did not ($n = 33$) have polyneuropathy compared to healthy controls ($n = 35$). The authors found no differences in vHIT values among the three groups.

Research studies have suggested the localization of injury within the vestibular organs and their pathways based on cVEMP abnormal findings. They suggested that reduced P1-N1 amplitude is due to labyrinthine pathology, while prolonged P1 and N1 latencies are due to retrolabyrinthine pathology[16]. Murofushi *et al*[16] observed prolonged P13 of cVEMP (*i.e.* slow conduction) with multiple sclerosis and large acoustic neuroma, suggesting brainstem pathology secondary to demyelination in the vestibulo-spinal tract.

We reported dizziness in few patients (10%, $n = 6$). They had unilateral prolonged P1 and N1 latencies and reduced P1-N1 amplitudes. In accordance, Biurrun *et al*[3] did not report dizziness or imbalance with diabetes. Gawron *et al*[4] reported dizziness and imbalance in only 6.3%. It has been observed that vestibular manifestations occur with unilateral lesion or asymmetrical bilateral lesions[3-9]. Diabetes is a metabolic systemic disease. The symmetrical bilateral inner ear dysfunction is the most acceptable explanation for the lack of vestibular symptoms with bilateral compared to unilateral lesions[3,4].

We observed differences in VEMP changes in relation to diabetes duration (*i.e.* > 5 years *vs* ≤ 5 years), severity of diabetes (*i.e.* HbA1c $> 7\%$ *vs* $\leq 7\%$), presence of absence of complications (*i.e.* DKA, hypoglycemia, peripheral neuropathy, *etc.*) and clinical symptoms (*i.e.* dizziness). However, the results of regression analysis showed that the only predictors for vestibular dysfunctions were chronic and severe diabetes. In accordance, Bektas *et al*[6] found no significant difference in cVEMP results between patients with T2D [with ($n = 25$) or without ($n = 25$) peripheral neuropathy] and healthy controls ($n = 21$). Kamali *et al*[7] found prolonged cVEMP latency with T1D and had polyneuropathy, an indication of disease severity.

DM is chronic metabolic disease and a common vascular risk factor. Chronic hyperglycemia causes (1) Tissue injury by advanced glycation end products and oxidative stress factors. Also, the toxic injury to connective tissue results in thickening of the vascular walls and macro- and micro-angiopathies[17,18] and demyelination of the nerves[17]. Kocdor *et al*[18] found selective reduction in type I vestibular hair cells (sensory epithelia) with diabetes. Myers *et al*[17] found large disrupted portions of myelin sheath lamellae of the vestibular and auditory nerves in induced diabetic rats. They also found thinning of the myelin sheath and smaller axonal fibers' diameters, indicating oxidative stress injury; and (2) Alterations of inner ear fluid metabolism. Some suggested that the homeostasis of vestibular structures is very sensitive and rapidly injured by diabetic metabolic disturbance[19].

The strength of the study is the direct evaluation of the function of the saccule and its connections in children with T1D. However, this study has limitations: (1) Small sample size, however, this is an exploratory study done on nationally understudied population; and (2) The cross-sectional study design. Further longitudinal large sample size studies from children with T1D are required to determine the temporal relationship between the development of clinical and objective vestibular and/or auditory manifestations.

CONCLUSION

The results of the study provide evidence for the frequent injury of the saccula of the inner ear and its central pathway with T1D. Predictors for vestibular dysfunction are chronic and severe diabetes. As vestibulopathy is a common comorbid cause of impaired gaze and postural stabilities with diabetes, glycemic control is important to prevent vestibular diabetic complications.

ARTICLE HIGHLIGHTS

Research background

Integrity of vestibular organs and their reflexes is critical for maintaining balance in static condition and during motion and gaze stabilization. In healthy individuals, the brain organizes and integrates information from vision, proprioception and vestibular system. Diabetes is a common chronic metabolic/systemic disease. It causes complications in every organ of the body, especially the eyes, kidney, nerves, heart and blood vessels. Experimental and clinical studies provide evidence that peripheral and/or central auditory and/or vestibular systems' dysfunctions are common complications of diabetes. The mechanism of diabetic vestibulopathy is complex and still has to be explored. It may be related to diabetic complications or its comorbid conditions. It may also be due to alteration of inner ears homeostasis due to diabetic metabolic alterations associated with poor glycemic control.

Research motivation

Vestibulopathy is a known complication in adults with diabetes. The research hotspots include (1) Identification of the spectrum of vestibular and auditory manifestations due to diabetes mellitus and their predictors; (2) Understanding the temporal relation between the onset of diabetes and the development of auditory or vestibular manifestations; and (3) Determining whether diabetes itself and/or its comorbid medical conditions are causes of auditory and vestibular complications.

Research objectives

In children, this is the first study that systematically estimated the prevalence and predictors of vestibular injury or dysfunction with type 1 diabetes.

Research methods

Cervical vestibular evoked myogenic potential (cVEMP) type of VEMP testing was used for assessment of the saccular function of the otolith organ and its pathways.

Research results

Bilateral changes in cVEMP abnormalities are more frequent than unilateral. They are associated with chronic and severe diabetes.

Research conclusions

Injury of the saccule of the inner ear and its central connection occurs with type 1 diabetes.

Research perspectives

Multidisciplinary team is required to follow up regularly children with diabetes for prevention and early identification and treatment of associated complications. The treating endocrinologists have to optimize management of diabetes and its associated comorbidities and complications.

REFERENCES

- 1 **Maahs DM**, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am* 2010; **39**: 481-497 [PMID: 20723815 DOI: 10.1016/j.ecl.2010.05.011]
- 2 **El-Ziny MA**, Salem NA, El-Hawary AK, Chalaby NM, Elsharkawy AA. Epidemiology of childhood type 1 diabetes mellitus in Nile Delta, northern Egypt - a retrospective study. *J Clin Res Pediatr Endocrinol* 2014; **6**: 9-15 [PMID: 24637304 DOI: 10.4274/Jcrpe.1171]
- 3 **Biurrun O**, Ferrer JP, Lorente J, De España R, Gomis R, Traserra J. Asymptomatic

- electronystagmographic abnormalities in patients with type I diabetes mellitus. *ORL J Otorhinolaryngol Relat Spec* 1991; **53**: 335-338 [PMID: 1784472 DOI: 10.1159/000276242]
- 4 **Gawron W**, Pospiech L, Orendorz-Fraczkowska K, Noczynska A. Are there any disturbances in vestibular organ of children and young adults with Type I diabetes? *Diabetologia* 2002; **45**: 728-734 [PMID: 12107754 DOI: 10.1007/s00125-002-0813-x]
 - 5 **Agrawal Y**, Carey JP, Della Santina CC, Schubert MC, Minor LB. Diabetes, vestibular dysfunction, and falls: analyses from the National Health and Nutrition Examination Survey. *Otol Neurotol* 2010; **31**: 1445-1450 [PMID: 20856157 DOI: 10.1097/MAO.0b013e3181f2f035]
 - 6 **Bektas D**, Gazioglu S, Arslan S, Cobanoglu B, Boz C, Caylan R. VEMP responses are not affected in non-insulin-dependent diabetes mellitus patients with or without polyneuropathy. *Acta Otolaryngol* 2008; **128**: 768-771 [PMID: 18568519 DOI: 10.1080/00016480701714251]
 - 7 **Kamali B**, Hajiabohassan F, Fatahi J, Nasli Esfahani E, Sarrafzadeh J, Faghihzadeh S. Effects of diabetes mellitus type I with or without neuropathy on vestibular evoked myogenic potentials. *Acta Med Iran* 2013; **51**: 107-112 [PMID: 23585317]
 - 8 **Konukseven O**, Polat SB, Karahan S, Konukseven E, Ersoy R, Cakir B, Kutluhan A, Aksoy S. Electrophysiologic vestibular evaluation in type 2 diabetic and prediabetic patients: Air conduction ocular and cervical vestibular evoked myogenic potentials. *Int J Audiol* 2015; **54**: 536-543 [PMID: 25529975 DOI: 10.3109/14992027.2014.971887]
 - 9 **Kalkan M**, Bayram A, Gökay F, Cura HS, Mutlu C. Assessment of vestibular-evoked myogenic potentials and video head impulse test in type 2 diabetes mellitus patients with or without polyneuropathy. *Eur Arch Otorhinolaryngol* 2018; **275**: 719-724 [PMID: 29330601 DOI: 10.1007/s00405-018-4873-z]
 - 10 **Mirka A**, Black FO. Clinical application of dynamic posturography for evaluating sensory integration and vestibular dysfunction. *Neurol Clin* 1990; **8**: 351-359 [PMID: 2193216]
 - 11 **Barrett KE**, Barman SM, Boitano S, Brooks HL. Chapter 10. Hearing & equilibrium. In: Barrett KE, Barman SM, Boitano S, Brooks HL, editors. Ganong's review of medical physiology. 24th ed. New York: McGraw-Hill, 2012
 - 12 **Chiles NS**, Phillips CL, Volpato S, Bandinelli S, Ferrucci L, Guralnik JM, Patel KV. Diabetes, peripheral neuropathy, and lower-extremity function. *J Diabetes Complications* 2014; **28**: 91-95 [PMID: 24120281 DOI: 10.1016/j.jdiacomp.2013.08.007]
 - 13 **Colebatch JG**, Halmagyi GM. Vestibular evoked potentials in human neck muscles before and after unilateral vestibular deafferentation. *Neurology* 1992; **42**: 1635-1636 [PMID: 1641165 DOI: 10.1212/wnl.42.8.1635]
 - 14 **Rosengren SM**, Colebatch JG. The Contributions of Vestibular Evoked Myogenic Potentials and Acoustic Vestibular Stimulation to Our Understanding of the Vestibular System. *Front Neurol* 2018; **9**: 481 [PMID: 30013504 DOI: 10.3389/fneur.2018.00481]
 - 15 **Akin FW**, Murmane OD, Panus PC, Caruthers SK, Wilkinson AE, Proffitt TM. The influence of voluntary tonic EMG level on the vestibular-evoked myogenic potential. *J Rehabil Res Dev* 2004; **41**: 473-480 [PMID: 15543465 DOI: 10.1682/jrrd.2003.04.0060]
 - 16 **Murofushi T**, Matsuzaki M, Wu CH. Short tone burst-evoked myogenic potentials on the sternocleidomastoid muscle: are these potentials also of vestibular origin? *Arch Otolaryngol Head Neck Surg* 1999; **125**: 660-664 [PMID: 10367923 DOI: 10.1001/archotol.125.6.660]
 - 17 **Myers SF**, Ross MD, Jokelainen P, Graham MD, McClatchey KD. Morphological evidence of vestibular pathology in long-term experimental diabetes mellitus. I. Microvascular changes. *Acta Otolaryngol* 1985; **100**: 351-364 [PMID: 4082974 DOI: 10.3109/00016488509126559]
 - 18 **Kocdor P**, Kaya S, Erdil M, Cureoglu S, Paparella MM, Adams ME. Vascular and Neuroepithelial Histopathology of the Sacculle in Humans With Diabetes Mellitus. *Otol Neurotol* 2016; **37**: 553-557 [PMID: 27050649 DOI: 10.1097/MAO.0000000000001018]
 - 19 **Mendelsohn M**, Roderique J. Cationic changes in endolymph during hypoglycemia. *Laryngoscope* 1972; **82**: 1533-1540 [PMID: 5053992 DOI: 10.1288/00005537-197208000-00016]



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