

Vestibular evoked myogenic potentials in patients with iron deficiency anaemia

Fatma Atalay¹, Murat Yaşar¹,
Tuba Uyanık², Sezai Sacid Anbar³

¹ Kastamonu University Faculty of Medicine, Department of Otorhinolaryngology, Head and Neck Surgery, Kastamonu, Türkiye; ² Kastamonu University Faculty of Medicine, Department of Internal Medicine, Kastamonu, Türkiye; ³ Department Audiology, Kastamonu Training and Research Hospital, Kastamonu, Türkiye

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Correspondence

Fatma Atalay
E-mail: fatmatalay_88@hotmail.com

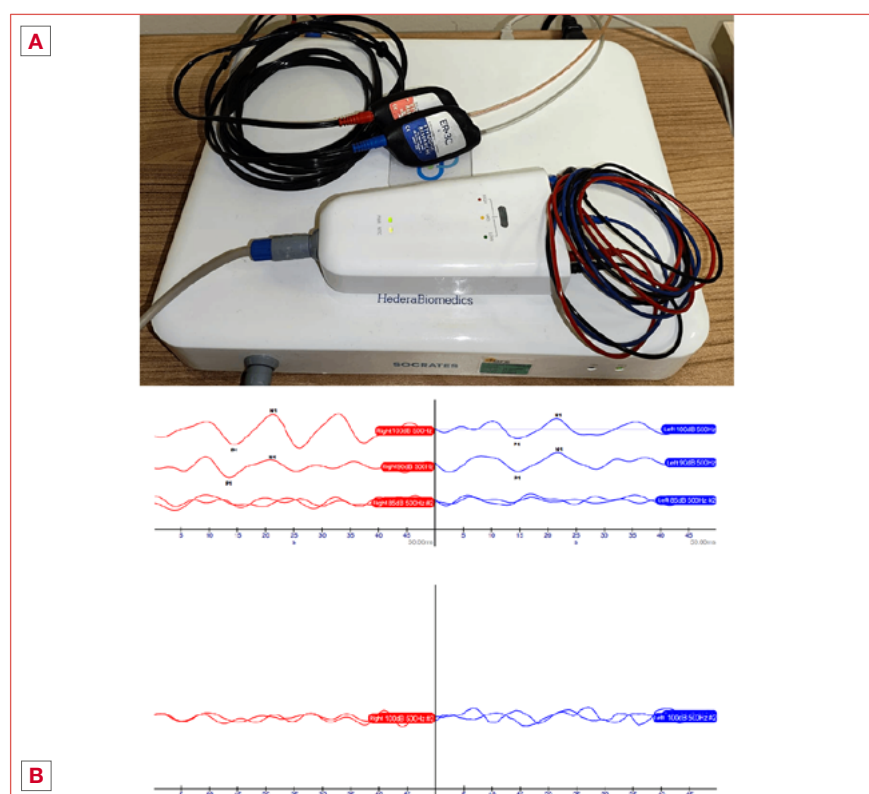
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Cover figure. Vestibular evoked myogenic potentials (VEMP) device (A); normal and bilaterally absent cervical VEMP tests of patients included in our study (B).

Summary

Objective. The aim of this study was to evaluate vestibular functions using cervical vestibular evoked myogenic potentials (cVEMP) in patients with iron deficiency anaemia (IDA) and investigate the early detection of potential vestibular hypofunction.

Methods. In this prospective study, the cVEMP results of 34 adult patients diagnosed with IDA and with no vestibular symptoms were compared with those of 34 audiotically healthy controls. P1-N1 latency times, interpeak amplitudes, and amplitude asymmetry rates were analysed and compared between the groups.

Results. One hundred thirty-six ears of 68 participants, 34 patients with IDA and 34 healthy controls, were included in the study. There was no significant difference in age or gender between groups ($p = 0.180$, $p = 0.726$, respectively). The absent VEMP response rate was significantly higher in the IDA group than in the control group ($p < 0.05$). No significant differences were determined between the IDA and control groups in terms of P1 latency, N1 latency, interpeak amplitude,

or threshold values ($p = 0.903$, $p = 0.407$, $p = 0.761$, $p = 0.729$, respectively). The asymmetry rate was significantly higher in the IDA group than in the control group ($p < 0.05$).

Conclusions. The increase in absent VEMP response and asymmetry rates in patients with IDA indicates that peripheral vestibular hypofunction has developed in these patients.

Keywords: iron deficiency anaemia, vestibular evoked myogenic potentials, vestibular system, hypoxia

Introduction

Iron deficiency anaemia (IDA) is the most common nutritional deficit and an important public health problem estimated to affect 30-50% of the world population. It is more frequent in children and women^{1,2}. The most common causes are decreased iron intake through diet or impaired absorption due to inadequate nutrition, gastrointestinal tract bleeding, and menstrual bleeding³. Diagnosis is based on laboratory findings, and oral or parenteral iron preparations can be used for treatment². IDA is a chronic and frequently asymptomatic condition. However, iron is essential for numerous cellular functions, such as enzymatic processes, oxygen transport, and mitochondrial energy production⁴. Non-specific symptoms such as hypoxia-related fatigue, weakness, lack of appetite, and pallor are therefore observed as the anaemia worsens. Central hypoxia-related headache, dizziness, and impaired neurocognitive functions can also be seen⁵.

Vestibular evoked myogenic potentials (VEMP) are a rapid, non-invasive, simple, and inexpensive muscular reflex test widely used to evaluate the superior and inferior branches of the vestibular nerve and otolith organs^{6,7}. VEMP measurement is divided into 2 components, cervical vestibular evoked myogenic potentials (cVEMP) and ocular vestibular evoked myogenic potentials (oVEMP), depending on the placement of the electrodes⁸. cVEMP is based on the vestibulocolic reflex and shows saccule and inferior vestibular nerve function through ipsilateral inhibition of the sternocleidomastoid muscle. oVEMP shows utricle and superior vestibular nerve function through contralateral stimulation of the inferior oblique eye muscle⁹. The presence or absence of a VEMP response, and the structure and asymmetry thereof, are a useful guide to determine the location of peripheral pathologies of the vestibular nerve¹⁰. VEMP abnormalities have been observed in vitamin B12 deficiency and in neurodegenerative diseases such as multiple sclerosis and vestibular migraine, diabetic peripheral neuropathy, and ankylosing spondylitis^{7,8,11,12}.

The purpose of this study was to evaluate vestibular functions using cVEMP in patients with IDA without vestibular symptoms and investigate the early detection of potential vestibular hypofunction.

Materials and methods

In this prospective study, the cVEMP results of 34 adult patients diagnosed with IDA (ferritin < 24 ng/mL, hemoglobin [Hb] < 12 g/dL in women; ferritin < 24 ng/mL, Hb < 13.5 g/dL in men) and with no vestibular symptoms were compared with those of 34 audiologically healthy controls, similar to the patient group in terms of age and gender, with no diagnosis of IDA or vestibular symptoms, with Hb = 13.5-17.5 g/dL and ferritin = 24-336 ng/mL. All participants included in the study underwent ear, nose, and throat examinations and cVEMP measurements. P1-N1 latency times, interpeak amplitudes, and amplitude asymmetry rates were analysed and compared between the groups. Individuals with histories of external or middle ear disease, vertigo, otological surgery, or using muscle relaxants were excluded.

VEMP recordings were made using a Hedera Biomedics Socrates (Italy) auditory evoked potential (AEP) device, with Ambu® Neuroline™ 720 (Denmark) surface electrodes and Sanibel (USA) electrode cables. A tone-burst stimulus at a frequency of 500 Hz was employed. The stimulus rate was 4.3/sec. Electromyographic filtering was determined as high pass filter 30 Hz and low pass filter 3000 Hz. The participants were asked to lie on a stretcher during the testing. The reference electrode was attached to the upper 1/3 of the sternocleidomastoid (SCM) muscle, the vertex electrode to the sternoclavicular joint region, and the ground electrode to the mid-forehead region (Fig. 1). All electrode impedances were lower than 3000 Ohms, and the difference in impedance between the electrodes was 1000 Ohms or less. The patients were asked to hold their heads in the air facing the opposite side of the ear being tested in order to achieve a sufficient level of SCM contraction. A resting period of at least 2 min was determined between each trace. The first significant negative and positive wave peaks were defined as N1 and P1, respectively. The interpeak amplitudes of the P1 and N1 waves were determined automatically using a Hedera Biomedics Socrates device. A 150 sweep was taken for each trace. In order to determine the VEMP threshold, the stimulus intensity was initially given as 100 dBnHL. If the trace exhibited the expected morphology, the traces were recorded by reducing the intensity by 10 dBnHL un-

til no VEMP responses were obtained. The final trace was recorded using 5 dBnHL increases to the intensity level at which no VEMP response was obtained, and the threshold was thus determined.

Statistical analyses were conducted using IBM SPSS Statistics version 26.0 software (IBM Corporation, New York, NY, USA). The distributions of the study data were examined using skewness and kurtosis coefficients and histogram charts. Parametric tests were applied for normally distributed variables and non-parametric tests for non-normally distributed variables. The Mann Whitney-U test and chi-square test were applied for data analysis. Statistics for the research variables were expressed as mean $\pm$ standard deviation. A p value < 0.05 was regarded as significant for all tests.

Results

One hundred thirty-six ears of 68 participants, 34 patients with IDA (20 women and 14 men), and 34 healthy controls (21 women and 13 men) were included in the study. Mean ages were 46.1 ± 15.8 years in the patients with IDA and 43.5 ± 10.6 in the control group. There was no significant age or gender difference between groups ($p = 0.180$ and $p = 0.726$, respectively).

The patient group consisted of patients with IDA (ferritin < 24 ng/mL and Hb < 12 g/dL in women and ferritin < 24 ng/mL and Hb < 13.5 g/dL in men). In the control group, Hb and ferritin levels were within normal limits (Hb = 13.5 – 17.5 g/dL and ferritin = 24 – 336 ng/mL). The members of both groups were audiotologically healthy, and their detailed ENT examinations were normal.

Examination revealed no cVEMP response (absent VEMP) in 21 members of the IDA group and in 4 members of the control group. Accordingly, the absent VEMP response rate was significantly higher in the IDA group than in the control group ($p < 0.05$) (Tab. I). No significant differences were determined between the IDA and control groups in terms of P1 latency, N1 latency, interpeak amplitude, or threshold values ($p = 0.903$, $p = 0.407$, $p = 0.761$, and $p = 0.729$, respectively). The asymmetry rate was significantly higher in the IDA group than in the control group ($p < 0.05$) (Tab. II).

Discussion

Iron is a highly important element involved in numerous biological functions, including oxygen transport, metabolic energy, deoxyribonucleic acid synthesis, and cellular respiration¹³. Oxygen transport capacity is impaired in IDA due to low Hb levels. Under such conditions, structures with high metabolism involving a greater oxygen requirement

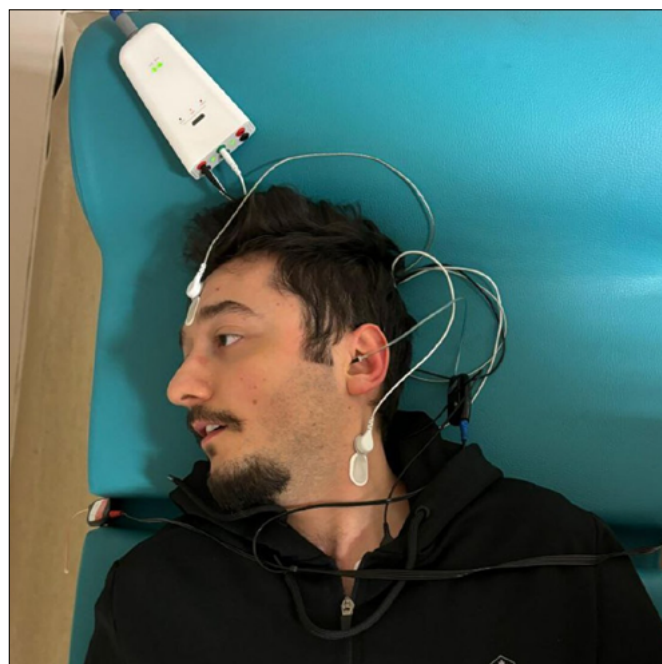


Figure 1. Placement of electrodes during cVEMP measurement.

Table I. Comparison of the presence of cVEMP responses.

Group	Presence of cVEMP responses				p
	Positive (n)	Absent (n)	Total (n)	Absent (%)	
IDA	47	21	68	30.8	0.000*
Control	64	4	68	5.8	
Total	111	25	136		

become more susceptible to anaemic damage and a potential risk of ischaemic stroke emerges¹⁴. The blood supply to the cochlea and the vestibular labyrinth is provided by the labyrinthine artery, which is a branch of the anterior inferior cerebellar artery (AICA). The labyrinthine artery is a terminal artery with minimal collaterals¹⁵. This renders the inner ear defenseless to ischaemia. A review study of anaemia in oncological patients reported that anaemia-related cerebral hypoxia can lead to headache, vertigo, dizziness, and tinnitus. These symptoms are frequently associated with underlying low levels of Hb¹⁶.

An electron microscope study investigating cochlear changes in iron deficiency observed alterations such as fusion and torsion in stereocilia, loss of stereocilia, and coalescence in iron-deficient rats. Since some cochlear enzymes contain iron, the findings suggest that this functional and structural

Table II. Comparison of cVEMP findings between groups.

Variable	Group	N	Mean	Standard deviation	Z	p
P1 latency	IDA	47	15.91	1.38	-0.122	0.903
	Control	64	15.94	1.87		
	Total	111	15.93	1.67		
N1 latency	IDA	47	21.50	1.48	-0.830	0.407
	Control	64	21.82	2.19		
	Total	111	21.68	1.92		
Interpeak amplitudes	IDA	47	177.62	86.13	-0.304	0.761
	Control	64	168.09	76.59		
	Total	111	170.65	81.67		
Threshold	IDA	47	93.91	6.90	-0.346	0.729
	Control	64	94.45	6.30		
	Total	111	94.22	6.53		
Amplitude asymmetry rate	IDA	34	59.75	40.24	-3.373	0.001*
	Control	34	25.47	27.13		
	Total	68	42.61	38.19		

impairment in the cochlea may derive from iron deficiency¹⁷. Due to the high metabolic needs of the hair cells, the cochlea is especially susceptible to ischaemic damage. Research has also shown that glycogen concentrations in hair cells is high and that glycogen decreases significantly in the face of hypoxia. Normal respiration must be maintained in order for glycolytic enzymes to be activated and function. In light of the role of iron in respiratory function, ischaemic damage is inevitable in case of iron deficiency¹⁸.

The VEMP test is a non-invasive procedure widely used in recent years to determine peripheral vestibular pathologies and to evaluate brain stem damage. Studies have observed VEMP abnormalities in diseases such as vestibular migraine, Meniere's disease, vestibular neuritis, vitamin B12 deficiency, multiple sclerosis, and some neurodegenerative diseases.⁷ Ulusoy et al. examined VEMP responses in patients with obstructive sleep apnoea syndrome (OSAS) and observed a decrease in those responses as the severity of OSAS increased. Those authors reported that repeated periods of hypoxia and reoxygenation in OSAS lead to oxidative stress and endothelial dysfunction, as well as activating the inflammatory cascade, and that the resulting hypoxia may produce adverse effects on the vestibular system and brain stem¹⁹. Absent VEMP response and asymmetry rates in the present study were also significantly higher in the IDA group than in the control group. This may be attributable to the peripheral vestibular end organs and vestibular nerve representing potential damage sites in hypoxia due to

iron deficiency. Therefore, it may be necessary to evaluate the peripheral vestibular system in patients with IDA. Demonstration of cVEMP abnormalities in patients with IDA with no vestibular symptoms shows that there is a decrease in peripheral vestibular system sensitivity in these patients and also shows that cVEMP can be used as a useful test in determining subclinical saccular and vestibular nerve pathologies at an early stage.

We encountered no previous studies using cVEMP to evaluate vestibular functions in IDA. Our research will thus contribute to the literature on this subject. Limitations of this study include that no evaluation was conducted according to the severity of the anaemia and that cVEMP responses before and after iron therapy were not examined. Further studies on the subject will make an additional contribution to the literature.

Conclusions

In conclusion, the increase in absent VEMP response and asymmetry rates in patients with IDA indicates that peripheral vestibular hypofunction has developed in these patients.

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Conflict of interest statement

The authors declare no conflict of interest.

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Author contribution

FA, MY, TU, SSA: conceptualization; FA, MY, TU, SSA: methodology; FA, MY, TU, SSA: validation; FA, TU: investigation; SSA, MY: data curation; FA: writing - original draft; MY, TU: writing - review&editing; FA, MY: supervision; FA, SSA: project administration. All of the authors have read and approved the manuscript.

Ethical consideration

Approval for the study was received from the Kastamonu University clinical research ethical committee prior to commencement (Decision no: 2023-KAEK-33, Date: 22.03.2023). All procedures involving human subjects were compatible with institutional (Kastamonu University Ethical Committee) ethical standards and the 1964 Declaration of Helsinki. Written informed consent was also obtained from all the patients taking part in the study.

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