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RESEARCH ARTICLE

Vestibular evoked myogenic potentials: early predictors of Alzheimer's disease?

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Abstract

Background and Aim: Recent studies have reported connections between vestibular function and cognition and also reported more prevalence of vestibular impairment in patients with Alzheimer's disease. Because patients with amnestic mild cognitive impairment (aMCI) are more likely to develop Alzheimer's disease, this study was conducted to evaluate vestibular dysfunction of otolith organs in aMCI patients compared to normal subjects.

Methods: In our case-control study, 11 patients (22 ears) with aMCI with mean age of 56.73 ±8.83 years and 11 normal participants (22 ears) with mean age of 54.30±7.4 years were evaluated for ocular and cervical vestibular evoked myogenic potentials (o- and cVEMP). Occurrence of VEMP responses, amplitude, latency and threshold of these waves were recorded and compared between the two groups.

Results: Ocular VEMP was absent in 63.6% of aMCI patients and in 18.2% of the normal group. The difference was significant (p=0.002), while occurrence rate, amplitude, latencies and threshold of cVEMP were not significantly different between the two groups (p>0.05). McNemar's test showed that there was no significant relationship between occurrences of two potentials in aMCI group.

Conclusion: These findings show the presence of vestibular dysfunction, especially in the pathways of ocular vestibular evoked potential, in patients with amnestic mild cognitive impairment. Given that previous studies have shown that cVEMP was absent in Alzheimer's disease, absence of oVEMP can be used as an indicator for predicting future impairment in individuals with amnestic MCI.

Keywords: Vestibular evoked myogenic potential; vestibular system; cognition; mild cognitive impairment

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Introduction

The vestibular system is composed of two major types of end-organs: the otolith organs and semicircular canals, which sense angular and linear acceleration of the head in three dimensions and is responsible for generating vestibulo-ocular and vestibulo-spinal reflexes. Moreover, research in both animals and humans has revealed the

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role of the vestibular system in cognition [1,2]. Several anatomic connections have been demonstrated between vestibular system and cognitive areas in the brain. Vestibular projections to higher levels include: parietal-insular and parietal-temporal cortex, and also medial-temporal cortex, including the hippocampus and parahippocampal gyrus. According to previous studies, patients with vestibular disorders have shown cognitive deficits such as memory impairment [1,3-6].

In early stage of Alzheimer's disease (AD), symptoms are most salient in the area of memory, particularly topographic memory, and are accompanied by specific degeneration of the hippocampal and parahippocampal regions of the medial-temporal cortex and hypo perfusion of the parietal-temporal and posterior cingulate cortices. In addition, vestibular abnormalities have been reported in AD patients. Considering the involved areas and prevalent vestibular loss in AD patients has led to the vestibular theory for AD. Based on the vestibular theory, AD can be an example of anterograde degeneration, in which destruction of lower structures leads to degeneration of their higher projection zones [1,7,8].

When AD is diagnosed, the neocortex has already been involved irreversibly. MCI is generally regarded as the borderland between the cognitive changes of aging and very early dementia [7,9].

These patients are divided into two major categories: if the patient with MCI shows memory impairment, MCI is amnestic MCI (aMCI) and if the patient does not have impairment in his/her memory and instead shows one or more defect in functions of language, attention, performance, spatial vision, and processing speed, nonamnestic MCI (nMCI) is existed [10]. It is reported that aMCI may progress to the Alzheimer's dementia and nMCI progresses towards non-Alzheimer's dementia [11-13].

While several studies have reported vestibular abnormalities such as low suppression rate of caloric nystagmus [14], absent cervical and ocular vestibular evoked myogenic potentials (c- and oVEMP) in AD patients [7,8], little information is available about vestibular function in patients diagnosed with MCI, particularly in patients with aMCI which may lead to AD.

Because of the difference in the clinical prognosis of aMCI and nMCI patients, we hypothesized the incidence of vestibular dysfunction observed in aMCI patients may be different from normal population. Keeping in this view, the aim of this study was to compare the otolithic function in patients with aMCI and normal individuals. In order to assess otolithic function, we recorded cervical and ocular vestibular myogenic potentials.

Methods

Eleven patients (8 female, 3 male) diagnosed with aMCI according to DSM V, Montreal Cognitive Assessment, and Rey Audio-Verbal learning test were enrolled in this study. The inclusion criteria were mini-mental state examination (MMSE) score<21, no history of diseases that cause MCI such as neurodegenerative and cerebrovascular diseases other than vestibular disorders, anxiety or depression, diabetes, active hypothyroidism, traumatic brain injury, Down syndrome, vitamin D and B12 deficiency, anticholinergic medication, alcoholism or drug abuse, and no cervical problem. Control group consisted of 11 healthy volunteers (6 female, 5 male) matched by age and level of education with aMCI group. They had normal cognitive function and their MMSE scores were higher than 21. All participants gave informed consent and the study was approved by Ethics Committee of Tehran University of Medical Sciences, Code No. IR.TUMS.FNM.REC.1396.4264.

Participants had normal otoscopic and tympanometric results and present acoustic reflexes at 500 and 1000 Hz. Myogenic potentials were recorded by Bio-logic Navigator Pro (Natus Medical Incorporated, Germany). The skin was cleansed and scrubbed with impedance lowering gel before placing the electrodes. For oVEMP recording, an active electrode was attached on 2mm below low eyelid, the reference electrode was attached on 2 mm below the active electrode, and the ground electrode was placed on

the forehead (Fpz). During testing, the participant was in sitting position and was asked to look at a target which was 30 degree upper than his/her eyes while he/she heard a sound on the insert earphone. Cervical VEMP was recorded with, active electrode on midpoint of sternocleidomastoid muscle (SCM), reference electrode on upper end of sternum and ground electrode on the forehead (Fpz). The patient was in supine position with the head away from the stimulated ear and was asked to elevate her/his head while hearing a sound on the insert earphone.

Sound stimuli presented through Bio-logic insert earphones as tone burst 500 Hz at 95 dBnHL. In oVEMP recording, 150 stimuli in alternative polarity with 100 K gain (rise/fall time=1 ms, plateau time=0 ms, 5.1 Hz repetition rate) were given to each ear. Responses were band passed 1-1000 Hz. We used 150 stimuli in rarefaction polarity with 5K gain (rise/fall time=2 ms, plateau time=4 ms, 5.1 Hz repetition rate; filter; 30-3000 Hz) to evoked cVEMP. Prior to each test run, impedance were measured from each electrode to ensure adequate electrode contact and symmetrical measures of impedance between electrodes. To control EMG activities in cVEMP recording, amplitude was rectified.

For the reliability, the tests were performed at least twice. To establish threshold, 10 dB decrements were used. Threshold was defined as the lowest intensity, which elicited response.

The outcomes of interest were oVEMP and cVEMP amplitudes, n10 and p15 latencies, p13 and n23 latencies, asymmetrical ratio of cVEMP and oVEMP, and presence of absence of waves. Mann-Whitney U test were used to compare means of amplitudes and latencies between groups. We used chi square test to compare occurrence of waves between groups. Relationship between presence of ocular and cervical VEMPs was analyzed using McNemar's test. SPSS 22 was used for statistical analysis. Significant level was set at 0.05.

Results

The study population included a total of 11 cases with aMCI and 11 normal cases. The mean age of aMCI group was 56.73 (SD=8.28) years (range 42-67) and 54.30 (SD=7.12) years (range 43-64) for normal group. Near 30% of aMCI patients have experienced vertigo at least once during their life, but it remained undiagnosed. None of normal cases had a history of vertigo.

In aMCI group, oVEMP was absent bilaterally in 6 (54.5%), absent in one ear in 2 (18.2%), and present in both sides in 3 (27.3%). In normal group, we recorded oVEMP 9 (81.8%). Two (18.2%) cases had no response in neither ears. Fig. 1 represents a sample of absent oVEMP in an aMCI patient and a sample of oVEMP recording in a normal participant. The occurrence of oVEMP was significantly lower in aMCI group (36.4% vs 81.8%, p=0.003).

In the recorded oVEMPs, other parameters such as latencies, amplitude and asymmetrical ratio did not differ significantly between two groups (p>0.05, Table 1).

Cervical VEMP responses were recorded bilaterally in 6 (60%) of the aMCI patients and in 10 (90.9%) of the control group. In aMCI cases, 3 (30%) showed unilateral absent response and 1 (10%) showed bilateral absent response. The occurrence of cVEMP and the wave parameters were similar to control group as shown in Table 1 (p>0.05).

There was not significant relationship between oVEMP and cVEMP occurrence (p>0.05).

Discussion

Alzheimer's disease is the main cause of dementia and one of the great health-care challenges of the 21st century [15]. The initial occurrence of behavioral and psychological symptoms of dementia is probably due to the involvement of brainstem and especially serotonergic nuclei, so the vestibular myogenic potentials can be used to evaluate brainstem (lesions above the vestibular nuclei) as well as peripheral and central vestibular system [7,16,17].

In our study, we found that the occurrence of oVEMP was significantly lower in aMCI group relative to normal subjects while cVEMP was not significantly different between groups. This

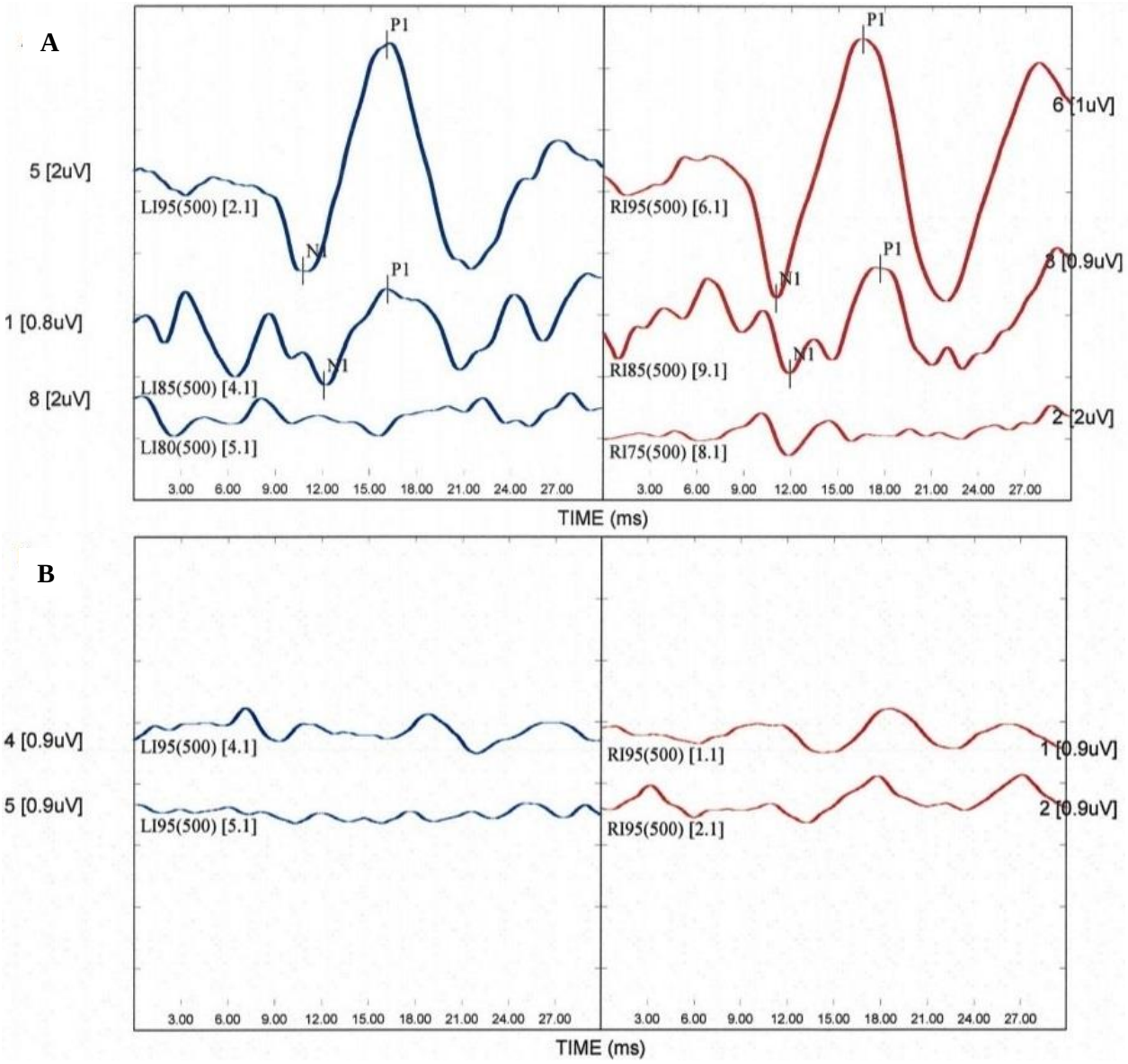

Fig. 1. A sample of A) bilateral present ocular vestibular evoked myogenic potential (oVEMP), B) bilateral absent oVEMP in a patient with amnestic mild cognitive impairment.

result indicates that vestibular impairment has started in aMCI patients with most abnormalities in oVEMP response.

Ocular VEMP represents the function of utricle, the upper branch of the vestibular nerve, and the vestibular nuclei which is located in the pons and medulla. The vestibular nuclei project to oculomotor nuclei via medial longitudinal fasciculus. The arc of the reflex is completed by oculomotor nerves and muscles [18]. The absence of oVEMP can be due to the abnormalities in any stage through the arc. Although a utricular lesion is probably the main reason for the absence of oVEMP, disorders of the other parts should be considered since Bidelmen et al. has recently showed the onset of high brainstem involvement in aMCI patients [19].

Previous studies have reported that patients with AD have vestibular dysfunction and their vestibular assessments have shown some abnormalities. Cervical VEMP response was absent in a

Table 1. Mean (standard deviation) of latencies, amplitudes, asymmetrical ratio, and thresholds of ocular and cervical myogenic potentials in amnestic mild cognitive impairment and normal groups

	Mean (SD)	
	Normal (n=18 ears)	**aMCI (n=8 ears)**
oVEMP		
n10 latency (ms)	10.99 (1.11)	11.44 (1.32)
p15 latency (ms)	16.77 (1.44)	16.62 (1.43)
Amplitude (µv)	5.41 (5.44)	3.99 (4.31)
Asymmetrical ratio	26.69 (21.71)	21.73 (7.53)
Threshold (dB nHL)	85.28 (5.28)	88.12 (5.3)
cVEMP		
p13 latency (ms)	16.39 (1.10)	15.80 (0.91)
n23 latency (ms)	23.52 (1.58)	22.53 (1.52)
Amplitude (µv)	172.49 (88.77)	154.87 (51.92)
Asymmetrical ratio	17.85 (13.61)	15.47 (8.81)
Threshold (dB nHL)	84.00 (4.47)	84.67(3.99)

aMCI; amnestic mild cognitive impairment, oVEMP; ocular vestibular evoked myogenic potential, cVEMP; cervical vestibular evoked myogenic potential

significant percentage of patients with AD and in others the amplitudes of waves were decreased, latency was prolonged in either p13 or n23 or both [7,8]. However, in our preclinical study, the occurrence of cVEMP wasn't different between aMCI group and normal group. It is likely that, this response will be eliminated at later stages and or at the time of AD occurrence.

Harun et al. reported results of oVEMP, cVEMP and video head impulse test (vHIT) from 15 patients with MCI. They noted that, no significant difference in oVEMP and cVEMP occurrence and their amplitudes and also in vHIT parameters between MCI and control group, which is in contrast with our findings [8]. This contradiction can be attributed to the lack of categorization of MCI patients. In our study, only patients with aMCI were assessed and other categories were excluded. Our inclusion criteria were based on the theory that amnestic MCI is the typical prodromal stage of dementia due to AD but another type of MCI is more heterogeneous and associated with vascular dementia, frontotemporal dementia and dementia with Lewy bodies [12].

Our study showed higher incidence of the oVEMP disorders in aMCI patients than the normal group. This finding implies that aMCI patients may need vestibular rehabilitation to improve vestibular and cognitive function if end organs are involved. In agreement to our findings, Shin et al. demonstrated a specific deficit in balance control in MCI patients compared with controls, and suggested balance exercise program with visual compensation training for improvement of cognitive function [20].

The current study had some limitations; first, this was a cross-sectional study of patients and normal group. Second, the number of cases was small. To clarify the extent of vestibular dysfunction in aMCI patients, it is necessary to verify these results in a larger sample size, and third, to investigate the complete vestibular function in aMCI subjects, semicircular canals should also be assessed.

Conclusion

Amnestic MCI patients -patients with more prominent Alzheimer's prognosis- have more vestibular dysfunction. In aMCI patients, oVEMP occurrence was lower, but not cVEMP. It seems that the lesion first involves higher brainstem, and then spreads to other regions and cortex. The findings of our study are consistent with association between vestibular loss and cognitive impairment. Further studies are necessary to evaluate the impact of vestibular treatments on aMCI prognosis.

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Conflict of interest

The authors declare that they have no conflict of interest.

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