ORIGINAL ARTICLE

Sympathetic Skin Responses in Patients with Migraine Vestibulopathy

Şenol Polat, Alev Uneri, Cuneyd Uneri

Department of Otorhinolaryngology, Balance Center Acıbadem University, Medical Faculty, Acıbadem Healthcare Group Neurology and Oncology Hospital, Istanbul, Turkey, (SP)
Department of Otorhinolaryngology, Marmara University, Medical Faculty, Istanbul, Turkey, (AU, CU)

Objective: To evaluate the sympathetic nervous system activity in patients with migraine vestibulopathy (MV) by assessing sympathetic skin response (SSR) from both hands and postauricular (PA) region.

Study Design: Prospective non-randomized study

Setting: Neurology and Oncology hospital

Patients and Methods: Twenty-four patients diagnosed as MV and 17 healthy control subjects were enrolled to this study. SSR was recorded with the contralateral electrical stimulation of the median nerve for both palmar and postauricular (PA) regions between attacks. The results were compared with those recorded from control healthy subjects.

Results: Palmar SSRs were obtained from all of the patients and control subjects and there was no statistically significant difference between control and patient groups. The entire control group demonstrated bilateral PA-SSRs. We recorded bilateral PA-SSR in 13 patients, but we could not obtain PA-SSR in 11 patients. There was a significant difference in mean PA-amplitude values (p: 0.0001) and insignificant difference in mean PA-latency values (p: 0.279) between control and responder patient groups.

Conclusion: Results of this study showed that SSR measurements of MV patients were either absent or lower than control subjects which could be interpreted as sympathetic dysfunction. Moreover, these results may present a new pathophysiological bridge between migraine and vestibular pathologies.

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Introduction

The association between migraine and vestibular manifestations suggests that they may have common mechanisms. Over the last years, a number of studies have contributed towards improving our knowledge of the relationships between migraine and vestibular disorders. The clinical association of migraine and vertigo has been supported by case control studies presenting with dizziness [1-3] inversely, vertigo were found to be more common in patients with migraine than in controls [2-4].

Central anatomical connections between vestibular nuclei and autonomic pathways have been demonstrated in animal models [5-7]. Previous studies have proposed that the autonomic nervous dysfunction could relate to the development of vertigo in some of these vestibular pathologies such as in Meniere’s disease and recent investigations have identified a clinical syndrome of chronic or recurrent dizziness that is thought to be caused by autonomic nervous system dysfunction [8-11]. Also a wide variety of clinical signs and diagnostic tests indicate the sympathetic nervous system (SNS) dysfunction in patients with migraine and these data consistently document a reduction in sympathetic function in migraine patients compared to non-migraineurs [12-15]. The SNS dysfunction was reported both in the headache-free period and during migraine attacks [12-15]. The inner ear has extensive sympathetic innervation [6,18]. The study of Yates et al. [6] showed vestibular inputs reaching nucleus tractus solitarius which participates in the sympathetic regulation and the study of Spoendlin et al. [16] showed an extensive adrenergic network in the lamina spiralis ossea and underneath the vestibular
sensory epithelia independent of blood vessels. Cervical sympathectomy had been undertaken to reduce inner ear sympathetic activity in the treatment of Meniere’s disease \[17\]. In this study, in patients with bilateral Meniere’s disease anterior stellate ganglionectomies were performed and it was concluded that sympathectomy was of benefit in relation to the preservation of hearing, that its value in tinnitus was doubtful, and that it had considerably relieved the main symptom of vertigo.

One of the methods for assessment of sympathetic fibers impairment in peripheral neuropathies as well as disorders of sympathetic system in other diseases is the evaluation of sympathetic skin response (SSR) \[18,19\]. This test especially evaluates the sudomotor function of unmyelinated sympathetic fibers \[18,19\].

In this prospective study, we aimed to evaluate sympathetic nervous system function in patients with migraine vestibulopathy (MV) by the use of SSR. It has been shown to be a reliable, simple, reproducible and non-invasive technique for the analysis of the sympathetic component of the autonomic nervous system \[20-24\].

**Material and Methods**

In this prospective study, 24 patients with MV and 17 healthy volunteers were enrolled to the study. Patients were being followed up at least for one year at Neurology and Oncology Hospital Otorhinolaryngology and Neurotology clinic, Balance center. The study protocol was approved by the ethical board of the hospital and the informed consent was taken from the patients and control subjects.

Patients suffered from their complaints from one year to seven years (average period of 3.5 years). After a detailed medical history, all patients underwent a complete otolaryngologic and neurologic evaluation, audiometric assessment, balance function tests including Fukuda stepping test, positional and positioning tests, electronystagmography (ENG) with warm- and cool-water calorics, and magnetic resonance imaging of the brain.

The diagnosis of MV was based on the algorithm proposed by Uneri et al. \[25\] using the criteria shown in Table 1, as follows; The patients were considered to suffer from migraine vestibulopathy if they had: at least one of the criteria from Group A with criterion 1 from Group B or with two criteria from Group B subclass 2 after exclusion of other causes of vertigo. There might be one of the criteria of group C. As an additional inclusion criteria, only the patients who had at least one episode of vertigo/dizziness accompanying with migraine headache were enrolled to this study. Patients with abnormal radiological findings and with other otorhinolaryngological, neurological and systemic diseases including Diabetes, neuropathies and psychiatric disorders were excluded.

**Table 1.** Criteria for the assessment of patients with migraine and vestibular symptoms

**Group A Criteria**

1. Dizziness
   a. Chronically ongoing dizziness (4 weeks up to several years)
   b. Episodic attacks of dizziness (in between few seconds to days)
   c. Continuous dizziness after vertigo attacks (more than 1 day)

2. Vertigo attacks
   a. Vertigo attacks with short durations (few seconds to 15 min)
   b. Classical vestibular attack (from 15 min to 72 h)

**Group B Criteria**

1. To fit at least one of the migraine definitions according to International Headache Society classification (2004).
   a. Migraine presence in first degree relatives
   b. Motion sickness (especially past history of childhood period)
   c. Low blood pressure; (causal SBP of < 105 mm Hg and/or DBP of < 60 mm Hg)

**Group C Criteria**

1. Without hearing loss
   a. Tinnitus or humming noise (uni or bilateral, continuous or with intervals)
   b. Pressure or fullness in the ear (uni or bilateral, continuous or with intervals)

2. With hearing loss
   a. Progressive sensorineural hearing loss
   b. Sudden sensorineural hearing loss

*Min: minute; h: hour; SBP: systolic blood pressure; DBP: diastolic blood pressure*

Before SSR test, the patients and volunteers were instructed not to consume coffee, tea or alcohol and were asked to refrain from smoking after midnight. All measurements were taken between 9:00 and 15:00.
The room was temperature controlled at 23-25°C, quiet, semi-darkened and comfortable, with minimization of arousal stimuli. Skin temperature was maintained above 34°C. Also patients and control groups were instructed to keep their eyes open, not to breathe deeply, cough, talk or move. SSR recordings were performed by an Esaote Myto II electromyography (EMG) machine. SSR recordings were obtained from both hands and from bilateral postauricular (PA) region in all groups.

In palmar region, the active electrode was attached to the palm and the reference electrode was attached to the dorsum of the hand, bilaterally. For recordings from PA region, electrodes were placed to the hairless area just behind the auricle on both sides. Recordings from PA region allowed us to compare the right and left sides. Yıldız et al. studied optimal recording location in this region on different healthy subjects and determined the area that was free of artifacts caused by pulse from nearby vessels or muscles such as sternocleidomastoid muscle [8]. Band pass filters were maintained between 0.1 and 1000Hz and the sensitivity was 0.5 and 1 mV, while sweep speeds ranged between 5-10s. Stimulation times were done separately and with randomized intervals in order to avoid habituation. The duration and intensity of the stimuli were kept at 0.1 seconds 100-300 V respectively. If there was no response, the intensity level was increased by 10 mA up to either until responses occurred or no response at the intensity level of 100 mA. When the amplitude was larger than 50uV and the latency was similar for at least two for the subsequent stimuli the SSR was accepted to be present. For the obtained responses, means of latencies and amplitudes were calculated and compared with contralateral side, with those obtained from palmar regions and with those of controls.

The latency and amplitude measurements in SSR were performed by the cursors of the EMG machine. Latency was measured with the sensitivity of milliseconds from the onset of the initial negative deflection, while the midpoints between the peaks of the negative and positive deflections were accepted as the amplitudes of SSR.

Statistical Analysis
Statistical calculations were performed with NCSS 2007 program for Windows. Besides standard descriptive statistical calculations (mean and standard deviation), Mann Whitney-U test was used in the comparison of groups and Wilcoxon test was used to compare and assess the left and right side values. Chi square test and Odds Ratio was performed during the evaluation qualitative data. The results were evaluated within a 95% confidence interval. Statistical significance level was established at p<0.05.

Results
Patients consisted of 17 women and 7 men ranging in age from 24 to 65 years old, with an average age of 40.5 years. The control group consisted of 10 women and 7 men ranging in age from 18 to 58 years old, with an average age of 38.5 years. There was no statistically significant difference between age and sex of the groups (p=0.701, p=0.424 respectively). In all of patients at least one migraine headache accompanying to at least one of the vestibular complaints of dizziness or vertigo were recorded in the medical history of the patients.

Episodic attacks of vertigo and dizziness were reported to be the chief vestibular complaints in these patients (table 2). 18 patients had demonstrated more than 2 vertigo attacks with different intervals in our follow-up period and most of them (17/24) were unsteady in these intervals. Only in 6 patients there was no vertigo attack history and the main disturbing complaints were recorded to be recurrent or chronic ongoing dizziness. We recorded that some of the attacks only involved either migraine headache or vestibular manifestations in the follow-up period. Vestibular work-up results were shown in table 3. Fukuda stepping test was abnormal with different degrees in 19 patients during vertigo attacks and at the interval periods. On ENG, 3 patients demonstrated 2 unilateral and 1 bilateral mild hypo activity to caloric tests, but none of them were higher than 20% and not interpreted as canal paresis. None of the VNG recordings were found to be typical for other well-known vestibular pathologies including benign paroxysmal positional vertigo. Positional and positioning tests with VNG revealed nystagmus in 6 patients; in four patients there was first degree horizontal nystagmus to one side, in two patients there
was rotatory nystagmus whose features were not similar to those is seen in benign paroxysmal positional vertigo and did not answer to canalith repositioning maneuvers.

Table 2. History of vestibular complaints

<table>
<thead>
<tr>
<th>History of vestibular complaints</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic ongoing dizziness (4 wks to several yrs)</td>
<td>6</td>
</tr>
<tr>
<td>Episodic attacks of dizziness (few seconds to several days)</td>
<td>14</td>
</tr>
<tr>
<td>Vertigo attacks of short duration (few seconds to several days)</td>
<td>9</td>
</tr>
<tr>
<td>Classical vestibular attacks (15 min to 72 h)</td>
<td>9</td>
</tr>
<tr>
<td>Imbalance and unsteadiness</td>
<td>17</td>
</tr>
</tbody>
</table>

Most of the patients showed more than one type of the symptom complex in the following up period.

Table 3. Vestibular work-up results

<table>
<thead>
<tr>
<th>Vestibular work-up results</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronystagmography</td>
<td>24</td>
</tr>
<tr>
<td>Abnormal</td>
<td>3</td>
</tr>
<tr>
<td>Unilateral</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
</tr>
<tr>
<td>Fukuda stepping test</td>
<td>24</td>
</tr>
<tr>
<td>Abnormal</td>
<td>19</td>
</tr>
<tr>
<td>Normal</td>
<td>5</td>
</tr>
<tr>
<td>Positional and positioning tests with VNG</td>
<td>24</td>
</tr>
<tr>
<td>Abnormal</td>
<td>6*</td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
</tr>
</tbody>
</table>

*: None of the positional evoked nystagmus and vertigo were typical to BPPV.

Audiologic studies were presented in table 4. One patient had bilateral moderate flat type sensory neural hearing loss (right 40 dB and left 50 dB), 1 patient had unilateral down-slopping sensory neural hearing loss (40 dB) and one patient had unilateral mild sensory neural hearing loss (30 dB). Findings were not typical to any other cochleovestibular disease. Magnetic resonance imaging of the brain was reported to be normal in all of the patients.

Table 4. Otologic symptoms and findings

<table>
<thead>
<tr>
<th>Otologic symptoms and findings</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral</td>
<td>2</td>
</tr>
<tr>
<td>Fluctuating</td>
<td>-</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral</td>
<td>3</td>
</tr>
<tr>
<td>Aural fullness</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral</td>
<td>-</td>
</tr>
</tbody>
</table>

Results of SSR tests were shown in table 5 and table 6. Palmar SSRs were obtained from all of the patients and control subjects and there was no statistically significant difference between right and left hands in each group for both mean latencies and mean amplitudes. Also there was no statistically significant difference for both mean latencies and mean amplitudes when we compared the palmar SSRs of patients with control subjects (p=0.112, p=0.880, respectively).

The entire control group demonstrated bilateral PA-SSRs. There was no significant difference between right and left PA-SSR recordings among the control group for both latencies and amplitudes (p=0.586, p=0.492, respectively). Bilateral PA-SSRs could be obtained only from 13 patients with MV. Among other 11 patients; in 6 patients there was no response on either side, in 4 patients there was no response on the left PA region and in 1 patient no response on right PA region. When we compared the responsiveness between the groups, there was statistically significant difference (p=0.0001) with Odds ratio of 32.14 for the patient group (table 7). In bilateral responder 13 patients, there was no statistically significant difference between right and left PA-SSRs for both mean latencies and mean amplitudes (p=0.972, p=0.753, respectively).

We combined the data of the right and left PA region in each group, because there was no any significant difference within the groups. When we compared the PA region mean amplitudes of patients with control subjects, we recorded statistically significant difference (p= 0.0001, table 6). The mean latencies of PA-SSRs recorded in bilateral responder 13 patients did not show statistically significant difference when compared to control group (p= 0.279).
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Discussion

Sympathetic skin response is a slow wave resulting from activation of the sudomotor sympathetic efferent fibers and it represents a potential generated in skin sweat glands [17-19]. SSR is well correlated with other autonomic function tests and its abnormality is documented in a variety of neurological disorders such as diabetic neuropathy and Parkinson's disease [21,22]. Two different evaluation attitudes of the SSR have been presented. The qualitative evaluation accepts only the absence of SSR as a pathological sign, but the risk of false negative results cannot be excluded with this evaluation [23]. The quantitative evaluation measures latency and amplitude parameters and accepts significant changes in these parameters as pathological signs [24,25]. However, with this evaluation...
there is a risk of false positive results due to intra-individual variation in the range of 2-44% for amplitude and 2-22% for latency according to different literature data [18-20]. But it is reported that, in good methodological conditions, SSR is a simple, reliable indicator of sympathetic sudomotor outflow in central and peripheral nervous system disorders [20,23,24].

Sympathetic skin response measurement from the PA region was studied by Yıldız et al. and in five of 21 patients both palmar and PA SSR measurements were simultaneously recorded [8]. Physiological or anatomical variations such as sweat gland density and skin thickness that may influence on SSR shape between right and left sides were not reported to be pronounced [8]. They compared SSR recordings on both sides of PA region and reported sympathetic hypofunction on the side of involved ear in patients with Meniere’s disease and suggested localized sympathetic dysfunction.

In this prospective study, we presented the hypo-responsive or absent PA-SSR results in patients with Migraine vestibulopathy that supports the idea that PA responses could reflect sympathetic activity of the labyrinth. The sympathetic innervation of the inner ear has two subdivisions: one from the stellate ganglion associated with blood vessels and the other from the ipsilateral superior cervical ganglion mostly independent from blood vessels [10]. The sympathetic fibers of the head and face also project from the superior cervical ganglion. In a study, the effects of botulinum toxin A was evaluated in the treatment of tinnitus, and the toxin was injected into three sites around the affected ears [20]. In that study, the aim was to block the autonomic pathway that was thought to play a role in the pathophysiology of tinnitus and it was suggested that botulinum toxin A could be used in tinnitus treatment [20]. The postauricular injection sites used in that study were similar to our recording location. So these clues may imply the basis that the responses could reflect sympathetic activity of the labyrinth.

In our study we studied both palmar and postauricular SSR in all groups in order to validate our results and thus to increase the power of study. Palmar SSRs were present in all of the patients and control subjects. There was no statistically significant difference when the palmar SSRs recordings were compared between patients and control subjects (table 5 and 6). We recorded bilateral PA-SSR in 13 patients, but we could not obtain PA-SSR in 11 patients. All the control subjects were bilateral responders and there was no significant difference between right and left ears (table 5). When we compared the PA-SSRs of 13 bilateral responder patients with healthy subjects, we detected significant difference in mean amplitude values (p=0.0001) and insignificant difference in mean latency values (p=0.279) that latencies were longer and amplitudes were smaller in the patient group. In 6 patients (25%) there was no response on either side and in 5 patients (20%) there was no response on one side making a total of 11 patients (45.8%, Odds ratio=36.14, table 7). We believe that this high ratio could not be explained as incidental finding and needs to be taken in consideration and the explanation for this finding could be the impaired sympathetic function in patients with MV.

The autonomic and vestibular systems are physiologically related since natural vestibular activity influences the cardiovascular system [6,27]. As an example, nausea, pallor, and sweating are autonomic sequelae common to vertigo attacks, demonstrating a direct vestibular influence on the autonomic nervous system. Also central anatomical connections between vestibular nuclei and autonomic pathways have been identified in rabbit, cat and rat [5-7]. Although the definitive evidence of an efferent autonomic influence on the vestibular system has remained elusive, recent studies have showed clinical evidences that vestibular symptomatology could occur in relation to autonomic nervous system dysfunction [8-11]. Some others have suggested that autonomic nervous system dysfunction played a role in the pathophysiology of Meniere’s disease and they concluded that autonomic nervous system dysfunction was rather the cause than the result of Meniere’s disease [8,9]. Therefore, it is not unreasonable to assume that a subgroup of patients with vestibular manifestations could have an underlying autonomic nervous system dysfunction including sympathetic hypofunction.

The clinical association of vestibular complaints and migraine has been noted since the 19th century publication by Liveing in 1873 [28]. Bramwell and McMullen in 1926 noted that many neurological symptoms including episodic vertigo associated with migraine headache might also occur without headache.
Over the last few decades clinical relationship between vestibular complaints and migraine has evolved from several patient-control series. The mere association of vestibular complaints and migraine is certainly insufficient to make the diagnosis of migraine vestibulopathy, as vestibular disorders and migraine have both a high prevalence in the general population. So various sets of diagnostic criteria have been proposed and the common properties of these classifications were developed on the demonstration of presence of the vestibular complaints and migrainous manifestations in a patient in whom other causes of vertigo were excluded.

The role of the autonomic nervous system function in the pathophysiology of migraine was well studied. Multiple independent studies have shown that supine plasma noradrenaline levels were significantly lower than controls in migraineurs during headache free periods. Also, investigators have suggested that a disturbance of the autonomic nervous system is a primary characteristics of migraine. These authors proposed that, during headache free periods, migraineurs have a reduction in sympathetic function when compared to nonmigrainours. In this study, we detected decreased or absent PA-SSR in patients who suffer from both migraine headaches and vestibular manifestations. These results and abovementioned studies lead us to propose that there might be a sympathetic dysfunction in patients who can develop clinical manifestations belonging to both migraine and vestibular pathologies. Moreover, results of this study may present a new additional pathophysiological bridge between migraine and vestibular symptomatology.

In conclusion, SSR measurements of MV patients were either absent or lower than control subjects which could be interpreted as sympathetic dysfunction. Therefore, sympathetic hypofunction may be one of the predisposing factors in patients with MV. Larger investigations are needed to fully validate this concept.

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Conflict of Interest
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References


