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Original Article

Association between Syncope and Tumarkin Attacks in Ménière's Disease

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OBJECTIVES: The aim of the current study was to further collect evidence that would confirm the hypothesis that vestibular drop attacks (VDAs) could cause syncope in patients with Ménière's disease (MD).

MATERIALS and METHODS: A cross-sectional survey design was employed in the present study. An Internet-based survey was administered on 602 individuals with MD. The mean age of the participants was 56.7 (25-75) years, and the mean duration of the disease was 12.4 (0.5-35) years.

RESULTS: VDAs with varying severity were present among 307 (50.7%) patients and led to fall in 92 patients, and syncope occurred in 45 patients with VDA. The overall percentage of syncope due to MD was 4.7%. Factors, such as duration of disease, age, and gender of the patient, did not explain attacks of syncope. Migraine and headache were not associated with syncope. Syncope was witnessed in 23 and self-reported by 22 patients. Syncope was associated with frequent VDA, duration of VDA, and falls that occurred during VDA. Patients with syncope reported the experience as frightening, had reduced general health-related quality of life, had higher anxiousness scores, and suffered more from fatigue. They also experienced problems with work, employment, and social restrictions.

CONCLUSION: Approximately 5% of patients with MD suffer from syncope, and syncope occurs among patients with VDA. In vestibular syncope, the sympathetic tone is lost, and baroreflex feedback is inhibited leading to fall and syncope. The consequences of vestibular syncope are severe, and patients face injuries and a significantly reduced quality of life.

KEYWORDS: Vasovagal attack, unconsciousness, vestibular syncope, tumarkin attacks, vestibular drop attacks, drop attacks

INTRODUCTION

Ménière's disease (MD) is characterized by recurrent vertigo, fluctuant hearing loss, and tinnitus. Patients with MD also often complain of gait problems, postural instability, and a sudden loss of balance, which are referred to as vestibular drop attacks (VDAs) or Tumarkin attacks [1, 2]. In his original report, Tumarkin [1] described the attack as follows: "One day (Mr. X) was standing at his desk talking to a client when suddenly he slumped to the floor. He had no vertigo, no loss of consciousness and no malaise. The thing came like a bolt from the blue, but he was able immediately to assure on lookers that he was alright and almost immediately got up and carried on" (p. 175). VDA is defined as a sudden alteration of lower extremity muscle tone. Jansen and Russel [3] described it as "the most distressing aspect of the attacks to the patients was the lack of warning and suddenness with which they occurred." The fall can be prevented by the patient searching for support in mild forms of VDA, whereas the patient may fall down to a lying position and may suffer injuries in more severe forms [5]. The prevalence of VDA leading to falls has been previously estimated to be as low as 6%-7% of patients with MD [2, 4]. The more recent estimation including the mild form indicates that VDA may occur among 72% of patients with MD [6]. The pathophysiology of VDA has been linked to sudden changes in the otolith function of the utriculus and/or sacculus due to change in pressure gradients within the inner ear [2, 7]. The utriculus is mainly responsive to horizontal plane linear accelerations, whereas the sacculus is mainly responsive to vertical plane linear accelerations, which occur when an individual falls downward. Prolonged space flight causes temporary disturbance in otolith function and has been associated with changes in orthostatic responses leading to fall and syncope indicating that the otolith organ is also involved in autonomic sympathetic reaction [8].

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Transient loss of consciousness is not an uncommon phenomenon in our society as 10.5% of subjects reported syncope in a follow-up study lasting for 17 years [9]. The European Heart Rhythm Association position paper defines "syncope" as a transient loss of consciousness due to transient global cerebral hypoperfusion and is characterized by rapid onset, short duration, and spontaneous complete recovery [10]. Recently, we showed that 12.3% of patients with MD have experienced syncope during their lifetime, and that there was a significant association of syncope with VDA, but the association was confounded by other reasons, such as vasovagal syncope and cardiovascular and cerebrovascular disorders [11]. In another study, we demonstrated that 4% of patients with MD reported that syncope appeared in connection with VDA [12]. Our findings of syncope patients with MD were recently confirmed by other studies [13]. The mechanism for syncope in VDA was suggested to be due to sympathetic-vestibular reflex that could lead to orthostatic hypotension. In the elderly population, approximately 2% of syncope has been classified as unexplained syncope that was caused by a vestibular disorder [14]. Recently, the Classification of Vestibular Disorders of the Bárány Society provided suggestion for a consensus document for diagnostic criteria of hemodynamic orthostatic dizziness/vertigo to be included in the International Classification of Vestibular Disorders [15]. However, this definition demonstrates the outcome of orthostatic test, not, for example, spontaneous hemodynamic changes of a patient with MD with falls in VDA.

We have recently demonstrated six carefully controlled patients with MD and VDA with syncope and also self-reported history of vestibular syncope in MD in association with VDA from 961 patients [11]. The aim of the current study was to further collect evidence that would confirm the hypothesis that VDA could cause syncope in patients with MD.

MATERIALS AND METHODS

Study Design and Participants

The present study used a cross-sectional survey design. Permission was obtained from the Finnish Ménière Federation (FMF; Suomen Meniere-liitto) to contact their members, asking them to complete an extensive questionnaire on symptoms related to MD. Under Finnish law, this kind of survey study conducted in association with patient association does not require ethical approval. The electronic survey was conducted using the Internet via e-mails that were sent to 952 of the 1646 FMF members since the e-mail address was not available for the remaining 704 members. For non-responders, the call was repeated by e-mail four times and by telephone calls if necessary. A total of 602 individuals responded to the query. The mean age of the respondents was 56.7 (25-75) years. The mean duration of the disease was 12.4 (0.5-35) years. Participants included 477 (79.2%) females and 125 (20.8%) males with respect to the gender distribution of FMF.

Data Collection

The symptoms and consequences of the disorder were assessed using a 38-item questionnaire. Questions in the survey focused on impact, social economic aspects, and complaints of MD, especially related to VDA. In addition, there were six disease- and impact-specific assessments using a mixture of open-ended and closed questions. The impact of the disorder was rated on a four-step scale from no impact to severe impact. The question of syncope, which was defined as a sudden and transient loss of consciousness, subsiding spontaneously, and without localizing neurological deficit, was used as outcome criteria in the present study. The question on syncope in association with VDA was formulated as follows: loss of consciousness in connection with VDA. The question focuses that in a drop attack you have lost consciousness that is not related to any injuries caused by falling in the attack. We also asked the following in the question (choose one option): (1) I do not have drop attacks, (2) I have drop attacks but have not lost consciousness, (3) Yes, in my own opinion I have been unconscious during a drop attack, and (4) Yes, another person has witnessed that I have been unconsciousness during a drop attack. The diagnosis of migraine was based on previous medical evaluation mostly performed by a neurologist, and we also used a question to confirm the diagnosis of migraine: Do you have migraine that has been diagnosed by a physician?

Statistical Analysis

Descriptive statistics were explored. The non-parametric Kruskal-Wallis H test was performed to study the association between various symptoms and demographic variables. The logistic regression analysis was used to further explore the association between syncope and demographic details and also complaints of the disease. A p-value 0.05 was used for interpretation of statistical data for significance.

RESULTS

Frequency of VDAs

Of the 602 patients, 295 (50.7%) reported that they had had VDA. VDA led to tripping among 133 individuals and to a fall among 92 patients. From these 295 patients, 45 reported that they had experienced losing their consciousness (Figure 1). The overall percentage for VDA among patients with MD was 4.7%. Syncope was witnessed in 23 patients and was self-reported in 22 patients. The duration of syncope varied from a few seconds to a few minutes. In five patients, gentamicin was used to stop VDA and was effective in all to stop syncope but was not effective in two to stop VDA. Factors, such as age, gender, and duration of MD in patients with VDA, did not differ among those with and without syncope. The frequency of VDA with

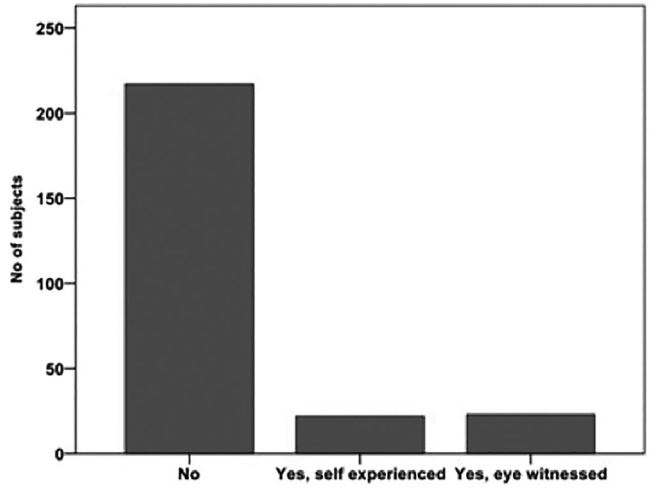

Figure 1. Number of patients with vestibular drop attacks classified as with or without syncope (n=45).

Table 4. Logistic regression model explaining syncope in vestibular drop attacks

						95% C.I. for Exp(B)	
Variables	**B**	**S.E.**	**Wald**	**Sig.**	**Exp(B)**	Lower	Upper
Hearing loss	0.786	0.405	3.77	0.052	2.194	0.992	4.850
Balance problems	-1.000	0.421	5.63	0.018	0.368	0.161	0.840
Absence of part of the visual field	0.659	0.384	2.94	0.086	1.934	0.910	4.107
Injuries during attack	1.295	0.263	24.24	<0.0001	3.652	2.181	6.115
Impact of social life	0.763	0.377	4.101	0.043	2.144	1.025	4.486
Constant	-8.129	1.390	34.18	<0.0001	0.000		

Table 1. Association of neurological complaints with attacks of syncope

Neurological complaints	**Chi-square**	**df**	**p**
Migraine	2.351	1	0.166
Headache	0.098	1	0.865
Saw tooth patterns in visual field	2.620	1	0.109
Moving spots in visual field	4.404	1	0.043
Absence of part of the visual field	15.766	1	<0.0001

Table 2. Association of factors leading to syncope in Vestibular Drop Attacks (VDA)

	Chi-square	**df**	**p**
Duration of episode in VDA	49.490	1	<0.0001
Frequency of episodes in VDA	47.647	1	<0.0001
Falls related to VDA	87.596	1	<0.0001
Injuries caused by VDA	60.396	1	<0.0001

Table 3. Impact of syncope in vestibular drop attacks on working capacity, social life and stress and anxiety

	Chi-square	**df**	**p**
Effect on quality working ability	65.376	1	<0.0001
Effect on social life	63.065	1	<0.0001
Stress/anxiety	50.413	1	<0.0001

syncope was relatively rare ranging from 1 to 6 attacks with a mean of 1.8 attacks in their whole MD history.

Association of Other Neurological Complaints with Syncope

The possible association of syncope with migraine, headache, and temporary visual impairments was examined using the Kruskal-Wallis test (Table 1). Results suggest that temporary visual impairments as moving spots in the visual field and especially the absence of segments of the visual field were significantly related to syncope. Migraine and headache were not associated with syncope. We further analyzed the possible association of syncope with migraine by dividing the patients into two groups: (a) those with no VDA and (b) those with VDA. Chi-square analysis showed that the outcome indicated that if the patient had had VDA, then syncope was associated with migraine (chi-square=11.274, df=2, p=0.004). However, no statistically significant association was observed with headache and VDA in the occurrence of syncope.

Association between Factors Related to VDAs and Syncope

Syncope in VDA had led to falls without injuries among 27 (60%) subjects. Syncope associated bruises with/without commotion occurred in 15 (33%) subjects. Six (7%) patients suffered from significant injuries. One patient had a severe back injury, one suffered from bone fracture, and one drove off the road. Based on the results of the Kruskal-Wallis test, syncope was related to a longer duration of VDA, greater frequency of VDA, falls in VDA, and injuries received from VDA (Table 2). Only two individuals reported that syncope occurred in connection with rotatory vertigo attack.

Social Consequences of Syncope Associated With VDAs

Patients with attacks of syncope rated poorer health-related quality of life (i.e., EuroQol EQ-5D-3L VAS instrument) than those without these attacks (t=2.022, p=0.044). The Kruskal-Wallis H test results suggested that attacks of syncope restricted the quality of working ability, impaired social life, and caused stress and anxiety (Table 3).

In a stepwise logistic regression analysis, syncope as a dependent variable, a model based on complaint history, was established (Table 4). In this model, balance problems between VDA, injuries during VDA, and impact of social life (i.e., social restrictions) were the factors contributing to the prediction of syncope. The model explained 18% of the variability of attacks leading to syncope.

DISCUSSION

Previously, we have shown that 4% of patients with MD have syncope in connection with VDA, [11] and the respective number in this study was 4.7%. The lifetime prevalence of syncope among patients with MD was 12.3%, [9, 11] which indicated that there are other factors than VDA explaining syncope among patients with MD. The present study focused on the evaluation of the association of VDA with syncope. We found that 50.5% of the patients experienced VDA, but most of them did not lead to fall. However, syncope occurred in approximately half of patients with VDA leading to fall. Those who experienced syncope in connection with VDA did not have syncope in most attacks. Therefore, it may be unrecognized and undiagnosed unless queried in detail. It may be that syncope is even more prevalent among patients with VDA as typically vasovagal response often leads to retrograde amnesia as was also reported by the patients in the present study [16].

The consequences of syncope were significant. Syncope reduced the quality of life, social interaction, and working ability and induced injuries. In the present study, one of the subjects drove off the road, and in two others, the person sitting beside could prevent an ac-

cident during syncope attacks. One person had syncope attack on the stairs and broke both maxilla and wrists. Thus, the present study confirms the potential risk of syncope attacks for severe incidents and vice versa, and injuries during VDA were significant predictors for syncope with an odds factor of 3.7. In the USA, the annual rate of orthostatic intolerance-related hospitalizations is 36 per 100.000 adults, and from these idiopathic syncope cases, 35% were hospitalized [17]. Needless to say, otologic causes were not included in the diagnosis.

For vestibular syncope, the provoking factors were the frequency of VDA, duration of these attacks, and falls caused by these attacks. Our findings that the semicircular canal-derived rotatory vertigo attacks were rare (occurred in only two patients) and did not correlate with syncope were supported by animal experiments indicating that the canal responses do not activate the vestibular sympathetic reflex [17, 18].

Migraine can cause dizziness and vertigo and is overrepresented among patients with MD [19]. It is suggested that vestibular migraine could cause vertigo mimicking MD [20] and even autonomic nervous system dysfunction with syncope [21]. Previously, there is no objective measurement confirming or rejecting the diagnosis of vestibular migraine from inner ear disease causing vertigo and dizziness [22]. When studying the association of syncope with migraine in the present study, we observed that if the patient had VDA, then migraine was associated with VDA-related syncope. Migraine was not explaining syncope in our previous study due to other confounders [11]. Before drawing definite conclusions on the role of migraine in MD-associated syncope, it is important to further explore the coexistence of vertigo spells with migraine in MD and the possible autonomic dysfunction in VDA in triggering syncope. Such effort could be performed in patients with MD with continuous heart rate recording to evaluate possible cardiac arrhythmias or changes in heart rate.

Blurring of vision is a common finding not only in orthostatic intolerance leading to syncope [23] but also in patients with otolith dysfunction similar to the present study. The vestibular organ can trigger rather complex symptoms, such as loss of visual acuity, imbalance, fear of falling, fatigue, and cognitive and attention problems [24]. In the present study, patients with syncope also experienced more anxiety disorders. Anxiety disorders are common in patients with MD [24]. In addition to vestibular sympathetic reflex, the link between vestibular disorders and anxiety may be mediated through connections between the superior vestibular nucleus and the parabrachial nucleus, which in turn provides afferents to the limbic system [17].

Orthostatic reactions in astronauts during immediate post-flight period lead to syncope, and this process and recovery parallels with the recovery of otolith function [8]. VDA-associated syncope appears to be triggered from the primary otolith afferents that have polarization vectors close to the vertical axis of the head [25, 26]. Such diversity of the otolith responses has also been shown by other researchers [27]. We assume that due to this diversity of otolith responses, the attacks leading to syncope are originated in specific parts of the otoliths, i.e., measuring the vertical axis of the head, [25, 26] whereas otolith ailment in other parts of the vestibulum, and causing VDA, may not provoke syncope.

The control of blood pressure and vascular tone is complex (Figure 2). The feedback of blood pressure is mediated through the baroreflex, which transmits baroreceptor signals to the solitary nucleus and from there to the caudal ventrolateral medulla (CVLM) region and nucleus ambiguus. The vestibular neural trajectories (i.e., vestibular sympathetic reflex) also operate at the rostral ventrolateral medulla (RVLM) [28]. Ray [29] demonstrated that the interaction between the vestibular sympathetic reflex and the baroreflex is additive in humans. The vestibular sympathetic reflex aids to defend against orthostatic challenges in humans by increasing sympathetic outflow. Our hypothesis is that during VDAs, the input from the vestibular system to the RVLM and CVLM exceeds the physiological range, and an over lowering in the blood pressure is incapable of pumping sufficient blood to the brain. However, the details of the regulatory mechanisms and why the heart rate slows down leading to syncope in VDA are not known so far.

The therapeutic and preventive possibilities appear to be limited. Gentamicin therapy is the most common and provides relief from VDA in the majority of patients. Some patients with VDA are rather resistant to therapy. We interpret that individual variability in the therapeutic responses of gentamicin is due to poor penetration of gentamicin into the vestibulum through the oval window membrane ligaments [30, 31]. Cardio-specific beta-blockers may be beneficial as they inhibit the vestibular sympathetic cardioinhibitory reflex as has been suggested [23] and may be effective in such patients in whom autonomic nervous activity is altered as in some patients with migraine and VDA. In MD, calcium channel blockers, such as cinnarizine, have been widely used therapeutically, [32] although these drugs are not available in the market in Nordic countries. A future study should be conducted to evaluate the value of predictive tests for orthostatic

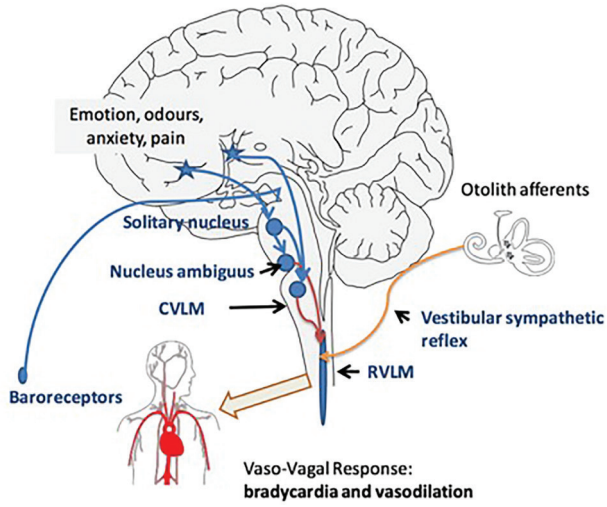

Figure 2. The suggested mechanism controlling heart rate and circulatory responses. The baroreceptors located in the large arteries respond within 1.5 s to changes in blood pressure. The baroreceptors convey information on heart rhythm and blood pressure to the solitary nucleus. From there, the cardio inhibitory responses traverse to the nucleus ambiguus and pressure data to the brain stem blood pressure nucleus. The blood pressure and blood circulation controls are located in the CVLM and collect data from these and also form the vestibular otolith input via the vestibular sympathetic reflexes via the RVLM. The outcome from the heart rate and blood circulation center is directed through different channels to the peripheral circulation and heart. Data are adapted from Yates and Bronstein [33], Guyton and Hall [34], Holstein et al. [35], and Raphan et al. [36].

intolerance in patients with VDAs, as previously we are not aware of any valid tests. We were not able to find any previous report investigating the association of VDA with migraine. A further study should be performed to reveal the coexistence of migraine with VDA and their suggestive association with syncope. In addition, in some patients with frequent syncope, a continuous heart rate monitoring could provide more information of autonomic dysfunction in VDA.

CONCLUSION

In MD, VDAs were prevalent in 50.5% of the patients. In most cases, it was rather mild. Failure in the otolith system in VDA leads to syncope in 14% of patients with MD probably through the erroneous activation of vestibular sympathetic response. The overall prevalence of syncope due to MD was 4.7%. The falls in VDA during syncope caused significant injuries to 7% of patients with MD. Syncope reduced the quality of life, impaired social life, and caused fatigue and anxiousness. Intratympanic administration of gentamicin should be prescribed to cure VDA, but may not be effective in all patients. Thus far, there are no valid tests to detect orthostatic intolerance leading to syncope among patients with MD.

Ethics Committee Approval: This study was conducted in collaboration with Finnish Ménière Federation. Under Finnish law, this kind of survey study conducted in association with patient association does not require ethical approval.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.P.; Design – I.P., V.M.; Resource – I.P.; Materials – I.P.; Data Collection and/or Processing – I.P.; Analysis and/or Interpretation – I.P., V.M.; Literature Search - I.P., V.M., J.Z., H.L., E.K.; Writing - I.P., V.M., J.Z., H.L., E.K.; Critical Reviews - I.P., V.M., J.Z., H.L., E.K.

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