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Vestibular syncope: A disorder associated with drop attack in Ménière's disease

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ABSTRACT

Objective: Experiments in humans and animals indicate that vestibular influx through vestibular sympathetic reflex is an important and vital part of the regulatory system of circulation. The otolith organ adjusts the circulatory responses through the vestibular sympathetic reflex during an upright stance and may trigger a vasovagal attack of syncope. The aim of the present study was to evaluate the prevalence and association of syncope attacks among patients with Ménière's disease (MD). Vestibular syncope was defined as a sudden and transient loss of consciousness, which subsides spontaneously in people with vestibular disorders and without localizing neurological deficit.

Methods: During clinical interactions, we encountered 5 patients with syncope during a Tumarkin attack of MD. Thereafter we evaluated data from 952 patients collected with a questionnaire from the Finnish Ménière Association (FMA). The data contained case histories with special attention to Tumarkin attacks, participation restriction, migraines, and syncope attacks. The mean age of the subjects participating in the study was 60.6 years (range 25–75 years). The duration of the disease was on average 9.8 years (range 0.5–35 years).

Results: In the current study sample, attacks of syncope were reported by 38 patients (4%) in association with the vertigo attack. Syncope was associated with Tumarkin attacks ($X^2 = 16.7$, $p < 0.001$), migraine ($X^2 = 7.4$, $p < 0.011$), history of ischemic heart disease ($X^2 = 6.0$, $p < 0.025$), and history of cerebrovascular disease ($X^2 = 11.7$, $p < 0.004$). Duration of MD was correlated with syncope. Syncope was provoked by physical strain and environmental pressure, and was associated with impairment of the visual field (i.e., visual blurring). In logistic regression analysis, syncope was significantly associated with Tumarkin attacks (odds ratio 3.2), migraines (odds ratio 2.3) and nausea (odds ratio 1.3). The attack of syncope was experienced as frightening, and general health related quality of life (HRQoL) was significantly worsened. Also, the patients suffered more from fatigue.

Conclusion: The current study indicates that patients with MD who suffer from Tumarkin attacks can suffer from syncope. It confirms the role of the otolith organ in controlling the circulatory homeostasis of the body. The actions are mediated through the vestibular sympathetic reflex.

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1. Introduction

Meniere's disease (MD) is an idiopathic, chronic disorder originating in the inner ear and is characterised by attacks of rotatory vertigo, hearing loss, and tinnitus/fullness of the ear [1]. The patients often also complain of gait problems, postural instability, and in a severe form, patients suffer from a sudden loss of balance often referred to as "drop attacks" or "Tumarkin attacks" [2,3,4]. In Tumarkin attacks, the patients typically report the sensation of being pushed, and they fall in the same direction with repeated falls [5]. In mild forms, the patient can prevent from falling by searching support, and in severe forms, they fall down to a lying position and may suffer injuries [6]. In the attack, the sudden slips or falls occur without warning, and without any concomitant neurologic symptoms or a sequel. The attacks are also linked to an abnormal ocular tilt of the environment simultaneous with the fall [5]. These attacks result from a sudden mechanical deformation of the otolithic membrane of the utricle or saccule due to abnormal pressure gradients within the inner ear [3,7].

Recent experiments on space flights indicate that the otolith input is an important regulator of blood pressure and heart rate, and may lead to syncope [8]. Experimental studies on animals indicate that the vestibular system projects to cardiovascular centres in the central nervous system through the vestibular sympathetic reflex and modulates blood pressure and heart rate in response to changes in the head and body position relative to gravity [9–16]. The anatomical connection of the vestibular sympathetic reflex pathway has been described in animals [17]. The activated cells in this pathway were concentrated in the caudal inferior and medial vestibular nuclei, otolith-recipient regions, and sent axonal projections to the rostral and caudal ventrolateral medullary areas [18]. These regions are integral parts of the sympathetic pathway to the spinal cord, ultimately leading to activation of the blood vessels and controlling the heart rate [19]. Some primary otolith afferents have polarization vectors close to the vertical axis of the head [20]. Yakushin et al. [21] demonstrated that during pitch oscillation, these neurons are activated as their orientation vectors pass through the spatial, vertical, and conveyan otolith-recipient signal to the central vestibular neurons. Among such central otolith-related neurons are those with orientation vectors close to the vertical axis of the head [22].

Normally in humans upon rising to a standing position, a vestibular sympathetic reflex is initiated in the vestibular system that operates in conjunction with the baroreflex to maintain stable blood flow in the central nervous system [16,23]. In animals, alteration of the vestibular sympathetic reflex can lead to orthostatic dizziness and even syncope due to a sudden drop in blood pressure [21]. The vasovagal response is comparable to the vasovagal attack observed in humans [19].

Recently, both diagnostic criteria of orthostatic intolerance leading to vasovagal syncope and its aetiology have been reinvestigated [24] and an increasing number of epidemiological studies have confirmed the role of orthostatic intolerance as a potent and independent risk factor in injuries and death (for review see Ref. [25]). Vasovagal syncope is a common event with up to 20% of all adults experiencing it by the age of 75. A critical feature of vasovagal syncope in humans and rats is the simultaneous occurrence of both bradycardia and hypotension at the onset of the syncope [26], which suggests a loss of baroreflex function [27,28]. The vasovagal syncope elicited in experimental conditions by vestibular stimulation is identical for the condition wherein the vestibular sympathetic reflex is activated [13].

We observed that in some patients, the Tumarkin attack was associated with syncope. In the present study, we systematically collected patients who had severe MD and who were hospitalized for syncope without any explanation. We also studied a large group of patients with MD to ascertain whether or not syncope is a prevalent symptom among patients with MD.

2. Method

2.1. Study design and study sample

During 2010 and 2016, patients with attacks of unconciousness were observed in a private clinic while participating in neuro-otological evaluations. A total of five patients met the criteria by having MD and suffering from one or more attacks of unconsciousness. All patients were referred to more detailed investigations including imaging studies of the head, internal medicine evaluation with ECG recording in suspected cases with a 24 h Holter recording. In addition, neurologists evaluated the patients with EEG recording.

Following this initial clinical observation, a prevalence study was conducted which used a cross-sectional survey design. To evaluate the association of syncope with vestibular disorder, 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. From 1646 members, the data was collected with a written questionnaire or with an Internet-based questionnaire. A written letter with a multipage questionnaire was sent to 1200 members of the society, and 740 members returned the questionnaire adequately filled. 446 members not included in the paper-based questionnaire were encouraged to reply on the Internet based questionnaire, and 221 members filled the Internet-based questionnaire adequately. The written questionnaire and Internet-based questionnaire were identical. Under Finnish law, this kind of study does not need ethical approval. The total sample was composed of 961 individuals (58.4%). 703 were females and 258 were males. Their mean age was 60.6 years (SD 13 years). Their MD-specific symptoms had lasted an average of 9.8 years (SD 5.1 years). Vestibular syncope was defined as a sudden and transient loss of consciousness, which subsides spontaneously in people with vestibular disorders and without localizing neurological deficit.

2.2. Data collection

A detailed 86-item otoneurology questionnaire was used for assessing the symptoms and consequences of the disorder [29–31]. The EuroQol EQ-5D-3L tool was used to study the general health-related quality of life (HRQoL) [32]. The EuroQol EQ-5D-3L tool has a test-retest reliability of 0.66 and

has validity in relation to other generic HRQoL measures such as the Short Form-36 (SF-36) [33]. Disease-specific impact assessment was done using a mixture of open-ended and closed questions. The questionnaire based on the ICF was used to classify the impact of the disease at the individual level [30]. Syncope was defined as a sudden and transient loss of consciousness, which subsides spontaneously and without localizing neurological deficit. The question on syncope was formulated as follows: "*When you have a vertigo attack, do you have these symptoms during the attack? Choose one or several options:* (1) *feeling of rotation;* (2) *feeling of floating;* (3) *tendency to fall;* (4) *instability when moving; and* (5) *becoming unconscious*". We used the question of unconsciousness as an outcome criterion in the present study.

2.3. Data analysis

Descriptive statistics were explored. Non-parametric tests such as Mann–Whitney U test and Kruskal Wallis H test were used to further analyze the data in order to explore the association between syncope and demographic details as well as complaints associated with the disease. The dependencies between factors were examined using the logistic regression analysis. A p-value of 0.05 was used for statistical significance interpretation.

3. Results

3.1. Case reports from the private clinic

We collected detailed case histories and interviewed 5 patients who were visiting emergency units because of unconsciousness in connection with MD (see Table 1). In all these patients, the unconsciousness was eyewitnessed either by spouse, ambulance personnel, or emergency unit personnel. One fell from a boat into the water and was rescued; one fell from a staircase and had broken a maxilla bone and wrist bone; one fell at home receiving bruises; and one fell in a shop. All had severe MD with Tumarkin attacks. Two of them had been with intratympanic gentamicin injections. In the emergency room and in later testing, no definite reason for attacks of unconsciousness was detected. In one person, the long term Holter recording is still to be carried out. In another patient, a transient ischemic attack was suspected, although there was no clinical or MRI verification of this.

3.2. Syncope with vertigo studied using a cross-sectional survey

Using questions asking for details of vertigo, we asked whether the patient had experienced loss of consciousness in connection with vertigo. The attacks of unconsciousness were reported in connection with vertigo by 38 subjects out of 961 subjects (i.e., 4%). The patients with syncope had a significantly longer history of MD ($t = 2.642$, $p = 0.008$). However, no differences between age and gender were observed (Fig.1).

In the Kruskal Wallis test, the attacks of syncope were significantly related to Tumarkin attacks and to the frequency of the Tumarkin attacks. The syncope was not associated with rotatory vertigo attacks nor other postural problems. However, it was provoked by mental pressure and physical exercise. It was also associated with nausea (see Table 2).

We also searched for association of syncope with headache and with neurological symptoms (see Table 3). Syncope was associated with migraine, blurred vision, and feelings of inebriation. Nevertheless, syncope was not associated with neurological complaints. The patients with syncope experienced fatigue. The syncope was correlated with migraine and tended to be associated with headache during the vertigo attack. The patients with syncope had a history of cerebrovascular insults and ischemic heart disease.

In logistic regression analysis, three items predicted significantly the syncope (see Table 4). The most important

Table 1
Case histories of unconsciousness among patients with MD. Frequency of Tumarkin attacks, rotatory vertigo attacks, age and duration of Meniere's disease, Gentamicin injections, visual problems during the attack, gait problems outside of the attack, and preliminary diagnosis of unconsciousness. Abbreviation: TIA = transient ischemic attack, R = right, L = left ear.

Patient no.	Tumarkin attacks	Rotatory vertigo attacks	Age and duration of MD in years	Treatment	Gait	Visual problems	Side of diseased ear	Preliminary diagnostic suggestion
599AK	Daily with falls	No	46 y, 12 y	Gentamicin injections: 3 times in Right ear	Yes	Problems with computer work	Right	No reason
600AML	Weekly	No	65 y, 25 y	Betahistine, Prochlorperazine	Yes	Visual saw tooth, spots, visual field absence	Right	Suspicion of TIA
602TH	Daily	Weekly	44 y, 6 y	Gentamicin injections: 5 times in Right ear and 8 times in Left ear	Yes, very severe	Problems with computer work	Right and left	No reason
587MB*	Monthly	Monthly	41 y, 2 y	Betahistine, Prochlorperazine	Yes	No	Left	Orthostatic hypotonia
594LAM**	Monthly	Monthly	38 y, 17 y	Betahistine, Prochlorperazine	Yes	Visual problems on focusing	Right and left	No reason

* At age 17 had migraine with visual aura. Ended after pregnancy at age 26.
** Horton's neuralgia, Holter recording is going on.

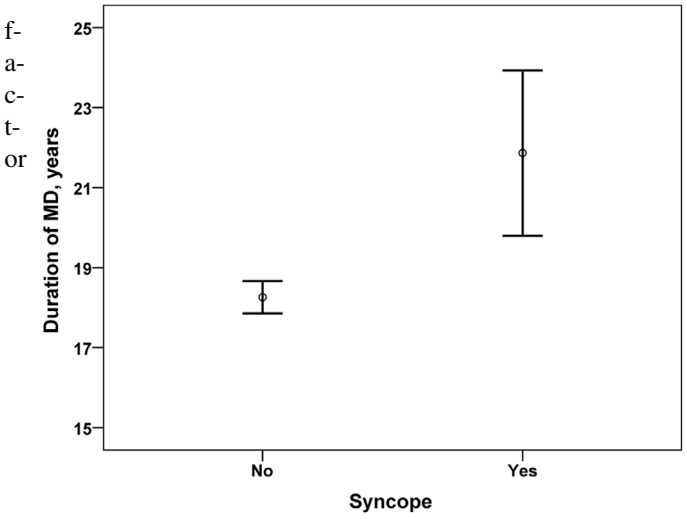

Fig. 1. Effect of duration of MD on prevalence of syncope ($t = 2.642$, $p = 0.008$).

was Tumarkin attacks ($p = 0.001$), followed by migraine ($p = 0.016$), and nausea ($p = 0.027$). The model could explain 9.5% of the variability of syncope in patients with MD.

3.3. Impact of syncope

Under questions asking details of impact of syncope, we asked whether the patient had experienced loss of consciousness (syncope) in connection with quality of life, mood and severity of MD. The syncope was associated with loss of energy and a worsened quality of life (see Table 5).

4. Discussion

The inability to maintain stable blood pressure during a position change is called orthostatic intolerance, which causes a drop in blood pressure [25]. The functional changes accompanying orthostatic intolerance can be understood as a temporal mismatch between cardiac output and vascular resistance [8,34]. In the present study, we report five patients identified with MD who had suffered from syncope during the Tumarkin attack. All were relatively young, and in a clinical following, no other disease explained the syncope. These observations initiated the current larger cross-sectional study. Among 961 patients with MD, 38 reported that that they had been unconscious during an attack of MD suggest that some of the drop attack with loss of consciousness is vestibular origin. In statistical work, the syncope attacks were associated with Tumarkin attacks, and in logistic regression analysis, Tumarkin attacks had carried an odds factor of 3.5 for syncope. Attacks of syncope reduced their HRQoL, and the patients experienced fatigue. It was more common in patients with a long history of MD, and was also associated with visual complaints. Calzada et al. [35] evaluated the association of otolithic membrane in patients with endolymphatic hydrops and came to the conclusion that the otolithic membrane was consistently damaged in patients with syncope, thus confirming histologically the importance of the otolith organ in attacks of syncope among patients with MD.

Among the German population, Radtke et al. [36] reported that orthostatic intolerance accounted for 42% of subjects with dizziness/vertigo and for 55% of non-vestibular dizziness diagnoses. However, as they were not able to classify a specific vestibular disorder, syncope was not included in this study and thus has not been reported in humans. In the present study, syncope was relatively rare among patients with MD as 4% of the patients had experienced syncope. However, we assume that syncope is more common as was reported. The patients will often have post-attack amnesia, not recalling whether they were unconscious or not [37]. When evaluating the origin of syncope, O'Mahony and Foote [38] demonstrated in the elderly that about 2% of syncope that they classified as unexplained syncope were caused by a vestibular disorder. No definite cause can be identified in nearly 40% of patients with moderate-to-severe classical orthostatic intolerance [39]. Maybe the vestibular organ associated with syncope has been misinterpreted or is quite rare. With the current numbers in mind, if the prevalence of MD is 513/100.000, then the true prevalence of vestibular syncope is about 25/100.000 [40].

Table 2
Association of vertigo complaints with syncope as indicated by the Kruskal Wallis test.

Symptoms	Chi-square	df	Sig.
Tumarkin attacks	16.72	1	0.0001
Frequency of attacks	6.49	1	0.011
Nausea	6.98	1	0.008
Environmental pressure change induced vertigo	6.26	1	0.012
Physical strain induced vertigo	4.26	1	0.039

Table 3
Association of neurological complaints with syncope examined using the Kruskal Wallis test.

Symptoms	Chi-square	df	Sig.
Migraine	7.376	1	0.011
Headache outside attacks	0.230	1	0.636
Headache during attacks	3.770	1	0.051
Feeling of being inebriated	6.820	1	0.011
Feeling that visual field is blurred	7.977	1	0.007
Absence of visual field during attack	1.894	1	0.226
Dysarthria or speech problems during the attack	2.297	1	0.154
Problems with swallowing during the attack	1.280	1	0.304
Paresis of any nerves during the attack	2.007	1	0.187
History of cerebrovascular insults	11.727	1	0.004
History of ischemic heart disease	6.017	1	0.025

Table 4
Outcome of logistic regression analysis on items explaining syncope in Meniere's disease.

	B	S.E.	Wald	df	Sig.	Exp (B)
Constant	−4.572	0.468	95.349	1	0.0001	0.010
Tumarkin attack	1.156	0.355	10.595	1	0.001	3.176
Migraine	0.870	0.363	5.750	1	0.016	2.386
Nausea	0.292	0.132	4.910	1	0.027	1.339

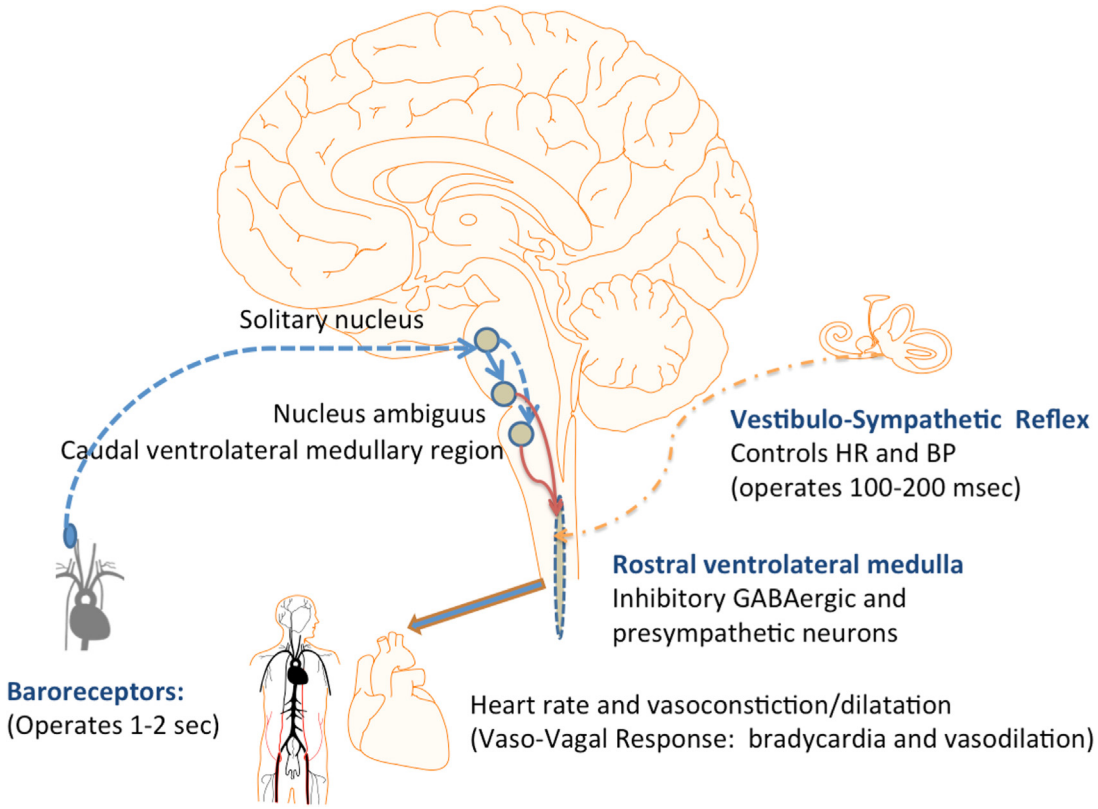

Fig. 2. The suggested mechanism controlling heart rate and circulatory responses. The baroreceptors located in the large arteries respond within 1.5 s to changes in blood pressure. The baroreceptors convey information on heart rhythm and blood pressure to solitary nucleus. From there, the cardio-inhibitory response travels to the nucleus ambigus and pressure data to the brain stem and blood pressure nucleus. The blood pressure and blood circulation control is located in the caudal ventrolateral medullary region (CVLM) and collects data from these and also forms vestibular otolith input via vestibular sympathetic reflexes. The CVLM gives rise to both excitatory and GABAergic inhibitory projections to the rostral ventrolateral medulla (RVLM), an area containing presympathetic neurons that innervate the intermediolateral cell column in the spinal cord. This pathway maintains homeostasis through constant negative feedback activity. The vestibular sympathetic reflex pathway was demonstrated from the caudal half of the spinal, medial, and parvocellular medial vestibular nuclei to the RVLM and CVLM. The outcome from the heart rate and blood circulation centre is directed through different channels to peripheral circulation and the heart (data adapted from Refs. [13,18,43,44]).

The origin of vestibular sympathetic reflex has been reported originally in animal experiments with sinusoidal galvanic stimulation of the vestibular system. In some animals, vestibular stimulation produced vasovagal syncope-like symptoms, including fatigue and uncoordinated movements or spontaneous falling [19]. With a similar stimulation system, Yakushin et al. [21] demonstrated that stimulation of the vestibular sympathetic reflex caused changes in peripheral resistance and cardiac output. Many studies indicate that cardiovascular responses to sinusoidal oscillation in pitch are of otolith origin [28,41,42]. Sympathetic nerve activity is modulated by otolith and not canal-related inputs [23]. The vasovagal influx arises from otolith neurons with orientation vectors close to the vertical axis of the head [21]. These neurons are likely to provide critical input to the vestibular sympathetic reflex to increase blood pressure and heart rate upon changes in head position relative to gravity and to contribute to the production of vasovagal oscillations and vasovagal responses and syncope when the baroreflex is inactivated (see Fig. 2). A critical feature of vasovagal responses in humans and experimental animals is the simultaneous occurrence of both bradycardia and hypotension at the onset of the vasovagal responses [26], which suggests a loss of baroreflex function [27,28]. Exactly how this baroreflex inactivation occurs, however, is unknown.

Table 5
Association of syncope with impact caused by Meniere's disease using the Kruskal Wallis test.

Symptoms	Chi-square	df	Sig.
Anxiety	2.48	1	0.116
Loss of energy	6.03	1	0.013
EQoL-VAS	1.99	1	0.158
EQoL-5D	4.74	1	0.030
MD-impact rating	2.85	1	0.092

In the present study, we found a significant association between syncope and migraine. In the paediatric population, migraine is the most common reason for syncope [45]. Also among adult females the migraine was associated with syncope [46] and carried a higher risk for ortostatic intolerance [47]. Curfman et al. [48] reported that nearly one-third of their recurrent syncope subjects met the criteria for syncopal migraine. Clinically they had similar clinical complaints as other migranours, and the anti-migraine treatment reduced syncope in half of the syncope migraine subjects. So far the clinical symptoms of migraine associated with vertigo have not been delineated. Nakada et al. [49] demonstrated that patients with migraine associated vertigo have endolymphatic hydrops in the

vestibular labyrinth but less seldom in the cochlea, whereas Guerkov et al. [50] demonstrated that 25% of patients had endolymphatic hydrops in both the vestibular labyrinth and cochlea. Migraine may also be associated with endolymphatic hydrops without vertigo, but with fluctuating hearing loss [51]. In MD, all patients will demonstrate endolymphatic hydrops [1,52]. Further studies are needed to evaluate the mechanism and role of migraine associated with endolymphatic hydrops and syncope. In the current study only one subject had tried beta-blocking agents but without any benefit against vertigo attacks.

Several epidemiological studies have confirmed the role of orthostatic intolerance as a potent and independent risk factor not only for syncopal attacks but also for total mortality and various conditions, such as coronary disease, stroke, heart and renal failure [25,53]. We observed that a history of cerebrovascular disease and ischemic heart diseases were associated with syncope. We tend to interpret that these disorders were provoking factors rather than a reason for syncope. Due to stiffening of the arterial walls and limited buffer capacity of the circulation, brain circulation becomes more intolerant for orthostatic pressure changes induced by positional strain. Ballester et al. [54] indicated among elderly patients with MD that drop attacks were highly prevalent (about 40%). The aetiology of drop attacks was liable to be misdiagnosed even if the symptoms and signs were consistent with MD [55]. Further studies are needed to evaluate the role of vestibular drop attacks in the elderly and the association of vestibular fault with other diseases. Noteworthy is that we found that in the elderly living in the elderly home about 10% had vestibular vertigo attacks and in half of the elderly suffering from balance problems had benign positional vertigo [56].

The consequences of Tumarkin attacks and syncope are frightening. In the present study, the quality of life measured with the EuroQoL EQ-5D-3L instrument was significantly worsened among patients with syncope. The patients with syncope were more fatigued. Loss of vitality has been reported as a consequence in patients with a vestibular orthostatic disorder [13]. These items should be taken into consideration during therapeutic efforts, although the therapeutic possibilities seem to be limited. Gentamicin therapy is the most promising and provides relief from Tumarkin attacks in 60–90% of patients [57,58]. However, two of the five patents in the present study were treated with gentamicin with limited efficacy. We interpreted this to the poor penetration of gentamicin through the oval window ligaments [59]. This may explain why some patients with Tumarkin attacks are quite resistant against therapy [60]. Cardio-specific beta-blockers may be beneficial as they inhibit the vestibular sympathetic cardio-inhibitory reflex as has been suggested [25]. Since the drop attacks are closely related to migraine, treating migraine may possibly benefit those with drop attacks. Treatment for migraine-associated syncope might be worth of trying but so far there is no validated treatment for that. The effect of beta blocking agents was nor beneficial in one patient (i.e., Table 1 patient 602 TH). Further work is needed to explore the treatment options for people with vestibular syncope.

The current study suffers from some shortages. First the syncope attacks among the 38 patients with MD in the larger study were not controlled for eye witness. As patients tend not to recall shot lasting syncope due to post syncopal amnesia the number of patients is probable greater than we reported here. We also did not evaluate vestibular evoked myogenic potentials (VEMP) among the patients. It may be so that VEMP is sensitive and in clinical cases it could point out which subjects with Tumarkin attacks are in risk of syncope. It may be so that utricular otolithic input rather than saccular one could actually impact the baroreceptor sensitivity and affect muscle and skin sympathetic nerve activity [61,62]. In this case the ocular VEMP could be useful as a predictor of the possible risk. A further study would be useful to investigate the association of Tumarkin attack with eyewitnessed syncope and to study the characteristics of Tumarkin attacks linked with syncope.

5. Conclusions

The vestibular system is controlling blood pressure during positional change via vestibular sympathetic reflex. The syncope accompanying orthostatic intolerance can be understood as a temporal mismatch between cardiac output and vascular resistance. Among 4% of patients with MD, attacks of syncope were associated with Tumarkin attack. A fault in otolith input due to Tumarkin attack seems to activate an erroneous vestibular sympathetic reflex leading to paradoxal inactivation of baroreflex, resulting in a syncope mimicking a vasovagal attack.

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