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Pyykko, Ilmari

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Original Article

Driving Habits and Risk of Traffic Accidents among People with Ménière's Disease in Finland

Ilmari Pyykkö , Vinaya Manchaiah , Jing Zou , Hilla Levo , Erna Kentala 

Department of Otolaryngology, Hearing and Balance Research Unit, University of Tampere, Tampere, Finland (IP)

Department of Speech and Hearing Sciences, Lamar University, Beaumont, Texas, USA (VM)

Department of Speech and Hearing, School of Allied Health Sciences, Manipal University, Manipal, Karnataka, India (VM)

Department of Otolaryngology, Head and Neck Surgery, Center for Otolaryngology-Head & Neck Surgery of Chinese PLA, Changhai Hospital, Second Military Medical University, Shanghai, China (JZ)

Department of Otolaryngology, University of Helsinki School of Medicine, Helsinki, Finland (HL, EK)

ORCID IDs of the authors: I.P. 0000-0001-7172-7408; V.M. 0000-0002-1254-8407; J.Z. 0000-0002-0315-7092; H.L. 0000-0002-8253-6065; E.K. 0000-0002-6031-3506.

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OBJECTIVES: The study evaluated the driving habits and risk of traffic accidents among people with Ménière's disease (MD) in Finland.

MATERIALS and METHODS: The study used a cross-sectional survey design. Members of the Finnish Ménière Federation (FMF) were contacted and requested to participate in an online survey. In total, 558 FMF members (58.7% response rate) responded to the survey.

RESULTS: People with MD were responsible for significantly fewer traffic accidents (0.8%) annually than individuals in the general population (1.7%). In addition, the lifetime risk of car accidents was lower among subjects with MD (8.3%) than that among individuals in the general population (24 to 28%). Nearly half of the total participants had either reduced the frequency of driving or had given up driving because of their condition. Factors such as gender, balance problems, visual problems with visual aura, and syncope during vestibular drop attacks can help explain the reasons for giving up car driving. One third (35.9%) of the participants were able to anticipate the MD attack before they decided to drive a car. Participants with falls during a vestibular drop attack, attacks of rotary vertigo, syncope during vestibular drop attacks, and those who were of a younger age were at a higher risk of experiencing a vertigo attack while driving a car. The most common strategies to avoid car accidents were selective driving and not driving when symptoms appeared.

CONCLUSION: The results show that people with MD are at a lower risk of traffic accidents than individuals in the general population, which can be explained by selective driving.

KEYWORDS: Ménière's disease, syncope, vestibular drop attack, driving habit, traffic accidents

INTRODUCTION

Ménière's disease (MD) is a condition that includes the inner ear manifested in episodic vertigo, hearing loss, fullness of the ear, and tinnitus. MD is a chronic illness affecting approximately 513 per 100,000 individuals^[1]. Majority of individuals with MD are over the age of 40 years, and MD is more prevalent among females than males^[2]. MD originates in the inner ear, although the etiology of the disorder is unknown^[3]. The condition has a long-lasting, but often unpredictable course, leading to functional limitations and restrictions and is not fully restored by medical therapy alone^[3]. MD is clinically diagnosed when an individual experiences at least two attacks of rotary vertigo (lasting at least 20 min), tinnitus, and hearing loss^[4]. This definition does not measure the impacts of postural and gait difficulties, unexpected vestibular drop attacks (VDA) sometimes leading to transient loss of consciousness, and other context-dependent problems, which create limitations disproportionate to the vestibular organ-specific^[5]. VDA is also referred to as Tumarkin attacks. In a broader context, MD also challenges a person's ability to drive a car because impairment of vestibular function may cause impairment of motion perception and spatial orientation as well as sudden falls, thus compromising the ability to safely drive a motor vehicle^[6,7]. Therefore, healthcare professionals have been concerned about the driving skills of their patients with MD for many years^[6-10], although there are no statistics showing increased accident rates for individuals with MD compared with individuals in the general population.

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Corresponding Address: Ilmari Pyykkö E-mail: ilmari.pyykko@tuni.fi

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The European Union directive for fitness to drive a vehicle provides few general rules for the medical health inspection. There are implications for hearing, vision evaluation, and neurological disorders. In the directive for driving license recognition and validity in health inspection, instructions on neurological diseases state: “Driving permission shall not be issued to, or renewed for, applicants or drivers suffering from a serious neurological disease, unless the application is supported by authorized medical opinion. Neurological disturbances associated with diseases or surgical intervention affecting the central or peripheral nervous system, which lead to sensory or motor deficiencies and affect balance and coordination, must accordingly be taken into account in relation to their functional effects and the risks of progression. In such cases, the issue or renewal of the permission may be subject to periodic assessment in the event of risk of deterioration”^[11]. This paragraph has been conceived in the United Kingdom and in Germany to mean that vertigo and dizziness (included in the evaluation), along with unpredictable balance problems, hinder a person’s ability to drive a car^[12]. In Nordic countries, that is, Finland, Sweden, Norway, and Denmark, no directive is required for the inspection of dizzy or vertiginous persons.

Currently, in MD, it seems that problems with car driving arise mainly when the vertigo is episodic, unpredictable, and especially in VDA, in which patients fall suddenly^[9, 10, 13, 14]. As previously discussed, the Driver and Vehicle Licensing Agency advice to doctors is vague: “Vertigo is a common condition and would rarely be severe enough to make driving unsafe”^[15]. Whether a patient should be advised to stop driving will depend on the doctor’s judgment of the impairment because it is difficult to fit consequences of vestibular derangement into the criteria^[7]. Although many doctors have counseled their patients, only few medical professionals have reported the vestibular patients to DLVA authorities^[7]. In addition, in a study by Parnes and Sindwani^[9], doctors living in the United States, where reporting was not mandatory, were more satisfied with their state’s legislation and were less likely to report patients as unfit to drive. This diversity in interpretation especially affects patients with MD. Driving a vehicle is a fundamental right and privilege and a virtual near-necessity for most people. MD has many adverse consequences on health (e.g., hearing difficulty and balance problems) and on psychological welfare^[16]. Social participation is a vital part of goal-directed behavior, forming the foundation of activities which become threatened by eventual restrictions of car driving. However, these restrictions may, at times, prove to be necessary because patients with MD assume that they are able to drive safely, when they may not, in fact, be able to do so^[10]. Considering the limited scientific literature in this area, this study was aimed to evaluate driving habits and risk of traffic accidents among people with MD in Finland.

MATERIALS AND METHODS

The study used a cross-sectional survey design, and the survey was conducted electronically using the internet. Permission was obtained from the Finnish Ménière Federation (FMF; Suomen Ménière-liitto ry) to contact their members, asking them to complete an extensive questionnaire on symptoms related to MD and car driving. As per the Finnish law, this kind of survey study conducted in association with a patient organization does not require ethical approval.

Participants

E-mails were sent to 952 of the 1,646 FMF members because the e-mail addresses of the remaining 704 members were unavailable. For non-responders, the call was repeated via e-mail four times. Completing an online survey was considered as providing informed consent. In total, 559 persons responded to the query (response rate of 58.7%). However, 11 had no driver’s license; therefore, the study group comprised 548 persons. The mean age of the respondents was 58.5 (range 23–87) years. The duration of the disease was 10.3 (range 1–54) years on average; 411 (75.0%) of the respondents were females, and 137 (25.0%) were males being consistent with the gender distribution of FMF.

Data Collection

A questionnaire was used for assessing the symptoms of MD, consequences of the disorder, car driving habits, and potential accidents and their consequences. The questions related to the impact of the disease were focused on social restriction and activity limitation, socio-economic aspects, and prodromatic complaints associated with MD. The impact of the vertigo complaints was rated on a four-point scale, from no impact, slight impact, moderate impact and severe impact. We also queried regarding the vestibular drop attacks, falls, and syncope related to VDA attacks in this study. Syncope was defined as a sudden and transient loss of consciousness, which subsides spontaneously and without neurological deficit. The questionnaire included several open-ended and structured questions that explored car driving habits and accidents, if any. For car accidents, we evaluated the time, reason, and consequences of the car accidents. We also asked about near-accident events and experiences. In addition, we questioned the subjects regarding their driving habits, how they ensured safe driving, and their work situation.

As discussed, the study was conducted in close collaboration with FMF. The questionnaire used was evaluated by 12 FMF board members for content appropriateness, and revisions were made based on their suggestions. FMF members will be informed regarding the study outcome through their monthly magazine.

Statistical Analysis

Descriptive statistics were first applied. The non-parametric Mann–Whitney U test and Kruskal–Wallis H test were performed to study the association between various symptoms and demographic variables. We used forward conditional logistic regression analysis to further explore the association between driving habits, complaints, demographic details, and restrictions associated with MD. In modeling the risk for driving in the stepwise analysis, we used a p-value of 0.10 to include in the model. However, a p-value of 0.05 was used for interpretation of statistical significance. Answers to open-ended questions were analyzed using the qualitative content analysis, and the frequency of the occurrence of each category was noted.

RESULTS

Severity, Frequency, and Duration of Vertigo Attacks

Of the 548 respondents, 175 (31.9%) participants no longer experienced vertigo; 13 (2.4%) experienced constant vertigo; 259 (47.4%) experienced episodic vertigo; and 101 (18.4%) experienced both episodic and constant vertigo. Rotary vertigo was experienced by

254 (46.4%) participants with MD. The severity of the vertigo spells was usually great in respondents who reported vertigo (see Figure 1). The vertigo attacks occurred less than once a year in 89 (16.2%) participants, less than monthly in 171 (31.2%), monthly in 56 (10.2%), weekly in 30 (5.5%), and daily in three (0.5%). In general, the average duration of a vertigo attack ranged from 20 minutes to 4 hours. However, in 126 (23%) participants, the duration of the vertigo attack was longer, lasting >24 hours.

VDA

Of the 548 participants, 228 (41.6%) participants had experienced VDA. Among the subjects with VDA, in 110 (48.2%) participants, the attack led to tripping, and in an additional 56 participants (24.6%), tripping led to a fall unless they found support from their immediate surroundings; 54 participants did fall, and of those, 42 participants suffered from injuries, mostly bruises. However, seven participants suffered from injuries in the head and on the face; five had fractures; and four had severe back injuries. Among participants with VDA, 31 (13.5%) participants had lost their consciousness. Three persons reported syncope in association with VDA while driving a car. In two cases, the subject sitting beside the study participant gained control over the steering wheel, thus preventing a car accident. One participant reported a severe car accident with multiple injuries.

Employment and Car Driving Habit

In total, 199 (36.3%) and 60 (10.9%) participants were working full-time and part-time, respectively; 19 (3.5%) were unemployed, 20

(3.6%) were on sick leave, 237 (43.3%) were retired, and 13 (2.4%) were on maternity leave or were newly enrolled in an education program. Participants with MD, who were still working, were significantly more likely to drive than the retired ones (Mann–Whitney U test, $Z=6.497$, $p<0.001$).

When evaluating the extent of car driving among the 548 persons with a driver's license, more than half (298 participants) drove daily, whereas 46 participants (8.4%) had voluntarily given up driving, and the additional 29 participants (5.3%) drove only when obligated (see Table 1).

Using the logistic regression analysis, we evaluated factors that may have contributed to the study participants' decision to stop driving a car. Significant factors in the model comprised gender (odds ratio 2.4), balance problems (odds ratio 3.0), visual problems with saw-tooth aura (odds ratio 1.9), and syncope during VDA (odds ratio 2.1). The variables were statistically significant, and the model explained 14.2% of the variability (see Table 2). The age of the respondents did not explain giving up driving (Student's t-test, $t=-0.702$, $p=0.483$). Interestingly, females drove less frequently than male participants (Mann–Whitney U test, $p<0.001$) and had given up driving more often than the male participants (Mann–Whitney U test, $p<0.014$).

Self-taken Preventive Procedures for Car Driving Hazards

We evaluated the kind of precautions the participants took before driving to ensure safe car driving. Noteworthy was that only 66 (12%) participants informed that they did not have any problems with car driving, and an additional 14 (1.8%) informed that they did not use any specific strategies for car driving, whereas 482 (88%) participants had at least some limitations and had to plan their car driving. Table 3 shows the replies to an open-ended question about the strategies used to ensure risk-free driving by study participants. Of the 548 participants, 80 participants (14.6%) did not report any strategies, whereas 228 (41.6%), 178 (32.5%), and 62 (11.3%) participants had reported one, two, and three strategies, respectively, to ensure safe driving. Notably, the most common strategy was not to drive when it became imminent that the vertigo symptoms would appear (nausea, vertigo, and balance problems). This strategy was present among 23.4% participants.

Ménière's Attack during Car Driving

Among 197 of the participants (35.9%), the vertigo spells had prodromes, allowing them to anticipate the attack before deciding to drive the car. The prodromes were observed usually 20 min–2 days before the attack. Figure 2 presents the types and frequency of prodromes in the study participants.

Logistic regression analysis was performed to identify factors that could explain and discriminate those experiencing a MD attack during car driving from those not experiencing an MD attack while driving (see Table 4). The model identified six factors that could predict the problems associated with an MD attack during car driving, and the model explained 15.3% of the variability. Participants who were of a younger age (odds ratio 1.01), were of the female gender (odds ratio 2.6), had experienced falls in VDA (odds ratio 1.3), had suffered attacks of rotary vertigo (odds ratio 1.6), or had syncope during VDA (odds ratio of 3.5) were at a higher

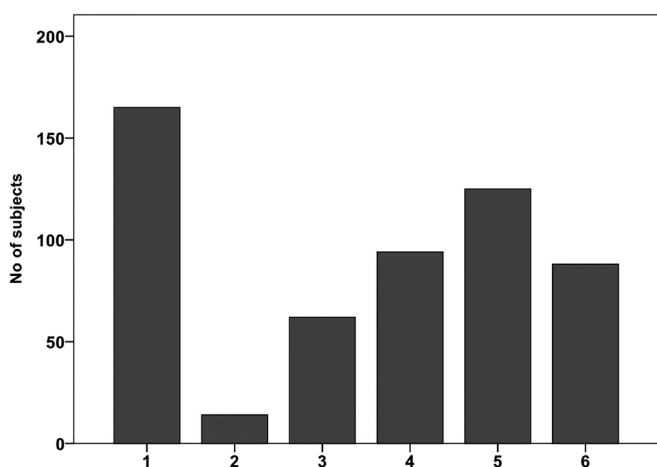


Figure 1. Severity of vertigo experienced by participants with Ménière's disease. 1=no vertigo, 2=mild (doesn't affect chores at all), 3=weak (affects but can continue working normally), 4=moderate (have to stop working), 5=strong (must rest) 6=very strong (difficulties despite rest).

Table 1. Driving habits among the participants with Ménière's disease

Extent of car driving	Number of subjects	Percentage (%)
I never drive	46	8.4
Only when absolutely necessary	29	5.3
Monthly	31	5.7
Weekly	144	26.3
Daily	298	54.4
All	548	100.0

Table 2. Logistic regression model explaining the factors that contribute to participants with Ménière's disease giving up driving a car

	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Gender	.893	.431	4.285	1	.038	2.441	1.049	5.684
Balance problems	-1.100	.354	9.629	1	.002	.333	.166	.667
Visual saw tooth	-.657	.349	3.550	1	.060	.519	.262	1.027
Syncope	.757	.207	13.420	1	.000	2.133	1.422	3.198
Constant	-2.613	.718	13.233	1	.000	.073		

The asymptotic distribution of the Wald statistic is chi-square with degrees of freedom equal to the number of parameters estimated.

Table 3. Strategies used by participants with Ménière's disease to ensure risk-free car driving

Strategy	First strategy (n)	Second strategy (n)	Third strategy (n)	All (n)	All (%)
I do not drive unless absolutely necessary	56	9	1	66	8.4
I do not drive when tired/I rest before driving	52	16	4	72	9.1
Not when sunshine dazzles	10	3	3	16	2.0
Not when I have even minor complaints or symptoms	22	8	1	31	3.9
Not in darkness/Not in rain	43	26	11	80	10.2
I avoid speed above 100 km/h	9	11	3	23	2.9
Not when symptoms appear (e.g., nausea, vertigo, balance problems)	139	39	6	184	23.4
Not without recommended drugs/therapy	15	4	5	24	3.0
I assure driving fitness by eye movement/gymnastic training	14	11	2	27	3.4
I have pauses during driving	7	5	6	18	2.3
I avoid head movements during driving	4	5	2	11	1.4
I use assistive devices of the car (adaptive cruise control, lane guard system etc)	9	0	4	13	1.6
I plan the journey beforehand	28	24	5	57	7.2
I avoid traffic rush period/ Not when in hurry	16	16	2	34	4.3
I am extremely careful	44	23	7	74	9.4
No problem at all with car driving/ I cannot say	80	0	0	66	10.2
Total	548	178	62	788	100

risk of experiencing a vertigo attack while driving a car. However, "problems with PC screen" were not found to be a statistically significant predictor.

Car Accidents and Near-Miss Accidents While Driving in Patients with MD

In the year 2016, 0.8% participants with MD in the current sample had experienced a traffic accident. The reference rate for individuals in the general population was 1.7% [17]. The lifetime traffic accident rate of participants with MD in the current sample was 8.3%. The reference rate for individuals in the general population was 28% for males and 24% for females in Finland [17]. Furthermore, near-miss accident situations during the entire lifetime were reported by 60 participants (10.9%); from these, 20 participants reported near-miss accident situations during the last year. The most common reasons for near-miss accident situations were as follows: vertigo, VDA, and visual misinterpretation (see Figure 3). The other reasons were unintentional lane changes, problems in the traffic roundabout, and sudden appearance of animals (e.g., a deer) in the

driving lane. When evaluating the near-miss accident situations, only visual problems with inspecting the PC screen were significant (p=0.044) determinants of near-miss accident situations [Exp(B)=0.57, CI=0.33-0.99].

The logistic regression model applied to the recent car accidents owing to MD yielded statistically significant results and explained 4% of the variance. In this model, gender was found to be a significant predictor (p=0.015), whereas the other two factors, including black spots in the visual field (p=0.072) and attacks of syncope (p=0.104), tended to be statistically significant (see Table 5).

DISCUSSION

In this study, we examined the driving habits and risk of traffic accidents among people with MD. This helped us understand if people with MD can drive cars safely and whether they pose risks for themselves and/or for others in traffic. A previous study has shown that drivers with epilepsy pose a two times greater risk of accidents than individuals in the general population [18]. The risk of deadly traffic ac-

Table 4. Logistic regression model explaining vertigo attacks of Ménière's disease while car driving

	Variables in the Equation					95% CI for Exp (B)		
	B	S.E.	Wald	df	Sig.	Exp (B)	Lower	Upper
Age	-.027	.009	9.918	1	.002	.973	.957	.990
Gender	-.940	.230	16.717	1	.000	.391	.249	.613
Problems with PC screen	-.390	.222	3.075	1	.080	.677	.438	1.047
Falls in vestibular drop attack.241		.103	5.426	1	.020	1.272	1.039	1.557
Attacks of rotary vertigo	.478	.218	4.798	1	.028	1.613	1.052	2.474
Syncope	1.254	.539	5.406	1	.020	3.503	1.218	10.079
Constant	-.902	.879	1.055	1	.304	.406		

Table 5. Logistic regression model explaining lifetime car accidents in participants with Ménière's disease

	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Gender	-.822	.336	5.969	1	.015	.440	.227	.850
Black spots in visual field	.576	.320	3.245	1	.072	1.780	.950	3.333
Syncope	1.086	.668	2.643	1	.104	2.963	.800	10.980
Constant	-3.818	.850	20.175	1	.000	.022		

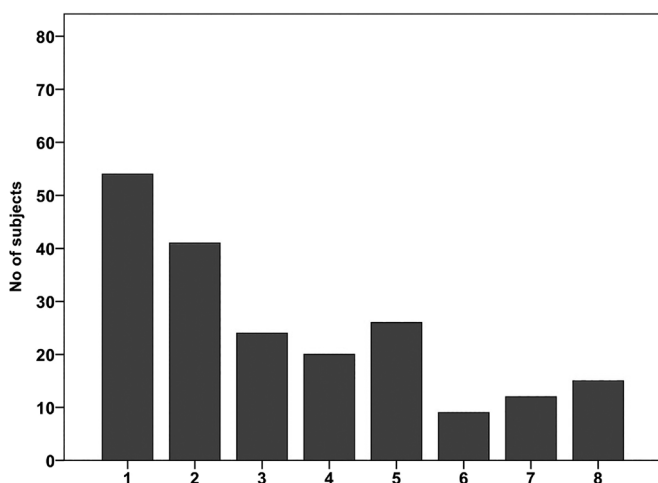


Figure 2. Types and frequency of prodromes for the vertigo attack in participants with Ménière's disease.

1=tinnitus, 2=pressure or fullness, 3=hyperacusis, 4=tiredness, 5=nausea, 6=visual problems, 7=gait, 8 = other.

cident because of drivers with cardiac disease is somewhat higher than of drivers with epilepsy [19]. In terms of the annual risk of traffic accidents, patients with MD had significantly fewer traffic accidents (0.8%) than individuals in the general population (1.7%) [17]. Furthermore, the lifetime risk of experiencing car accidents was lower among subjects with MD (8.3%) than among individuals in the general population (24%–28%) [17]. A possible explanation was that a significant proportion of the participants (11%) with MD had given up driving or practiced restricted driving. Approximately half (55%) of the participants with MD drove daily. In particular, retired patients drove much less frequently than working individuals. A second explanation for the low accident rate can be attributed to the effective management strategies used by drivers with MD. Majority of participants with MD (88%) used strategies such as driving only during the daytime, not

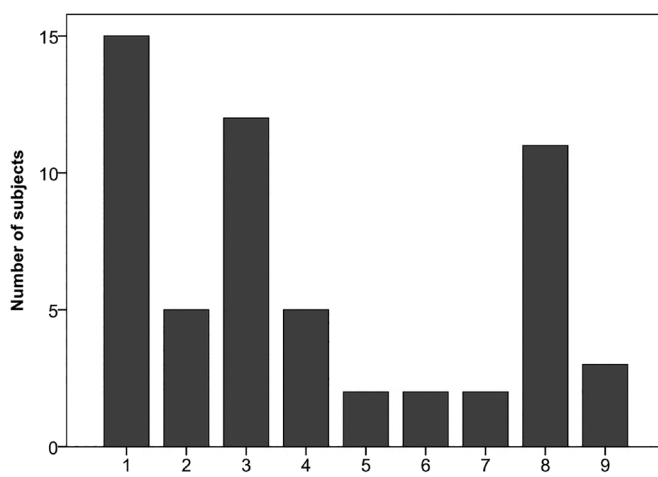


Figure 3. Near-miss accident situations while car driving, as reported by participants with Ménière's disease.

1=vertigo, 2=vestibular drop attack, 3=visual neglect, 4=other car, 5=sleepiness, 6=hearing, 7=pedestrian/bike, 8=lane or crossing situation, 9=animal, other.

driving when experiencing symptoms or when tired, reducing speed, and observing weather conditions.

This study showed that a high percentage of patients with MD experience VDA (41.6%). The prevalence of VDA in patients with MD has been previously estimated to be as low as 3%–7% [20, 21]. A more recent estimation indicates that VDA may occur in a less severe form among 49%–72% of patients with MD [22, 23]. The high incidence can be explained by the fact that the patients would probably not have spontaneously reported VDA that caused only mild or moderate disability if it had not specifically been inquired about [22, 23]. VDA are also associated with gait problems and postural instability [22, 23], although disequilibrium during an attack-free period or constant disequilibrium is encountered mainly during the later stage of the disease [24].

Driving Directives Concerning Vertigo in Different Countries

The driving directive is used in the European Union, in which the applicant agrees to meet the minimum standards of physical (especially visual acuity) and mental fitness [25]. The guidelines about vestibular disorders provided by the Canadian Medical Association state: “loss of the sense of balance can inhibit driving ability; therefore, normal functioning of the vestibular mechanism is essential” [26]. In Germany, the guidelines on requirements for driving are especially rigorous for vertiginous patients. The German Federal Highway Research Institute recommends several clinical tests to certify driving fitness of vertiginous patients. The attack-free interval of two years is required for MD patients without prodromes, and a period of three years for patients with vestibular migraine without prodromes. These strict restrictions for driving a vehicle have recently been opposed, especially by neurologists [10]. In the United Kingdom, patients with recurrent peripheral disorders (e.g., MD), who are subject to unexpected attacks of vertigo, should not drive any class of motor vehicle until their symptoms have been controlled. The doctor can only fulfill this obligation when they are aware of the patient’s driving history. However, it is suggested that the doctors tend to neglect investigating their patients’ driving history [7]. In the United Kingdom, to date, there are no medico-legal cases against doctors in severe accidents for car accidents involving vertiginous drivers. In the United States, 15% subjects with MD were advised against driving by their doctors, but they continued driving [11]. The Canadian General Medical Council has issued specific advice (after a court case) that the doctor must be confident that the patient understands their impaired condition to drive and that they should inform the Motor Vehicle Licensing Bureau about the health situation [9]. However, doctors have been negligent in reporting the driving limitations of their patients [9].

Vestibular Problems and Driving

Although there is no doubt that vestibular disease can impact safe driving, the restrictions and consequences of driving restrictions can be severe because it restricts social activities, impairs hobbies, and in urban environment, it may lead to unemployment. Subjects with MD have realized their limitations in driving a car and have developed at least one strategy to ensure safe driving. A common strategy was not to drive when symptoms are imminent (e.g., nausea, vertigo, balance problems), and this was used among a quarter of the subjects. The visual influx on balance and visual control of surroundings was disturbed in many subjects with MD, and they commonly restricted driving in sunshine, darkness, and rainy conditions. Cohen et al. [6] reported similar problems in subjects with MD; for example, people with MD become disoriented more easily than people without MD by extraneous visual stimuli or visual noise. These problems are reflected in their significantly difficult driving in conditions that reduce their visual acuity, such as at night or in the rain. Furthermore, driving during rush hours may be partly attributed to increased sensitivity to the motion of other objects in the visual field. The visual problems seem to be related to gaze stabilization and spatial orientation and egocentric navigation [27]. The type of vestibular guided navigation or path integration that is involved with the ability to stay in one’s lane while driving is impaired in people with vestibular disorders [6, 8].

There are only few studies that examine the fitness of people with MD to drive. Cohen et al. [11] studied 48 people with MD. In group comparison, there was no difference observed among people with

MD and individuals without MD in terms of the quality of driving. However, people with MD had more problems than individuals in the control groups when driving in challenging conditions. Therefore, most neuro-otologists and otologists in Switzerland do not allow a patient with VDA to drive [12]. This also follows the recommendation of McKiernan and Jonathan [7]. In this study, we recorded three driving incidents that were caused due to VDA. Based on our results, patients with visual orientation problems and VDA leading to falls and especially those with a history of VDA associated syncope should not be given permission to drive. Our observation has been recently introduced into medico-legal guidelines for fitness in driving (see <https://www.traficom.fi/>). However, the new medico-legal guidelines in Finland do not include any driving restrictions for patients with MD.

Limitations of the Study

The present exploratory analysis of car driving habits has a few limitations. First, we did not ask whether doctors have advised against driving because this would reduce the number of replies from those who should abstain from driving. These data would be interesting because in our practice, most patients with VDA, even with syncope, continue driving because they reside in urban areas. Second, the study involved the use of a survey design because the causes of traffic accidents are not tabulated as per traffic safety institutes or insurance institutes in Finland. Many participants may have problems recalling the exact events, and this may have introduced some bias. Third, this study did not consider how much (how many miles a year) MD patients are driving compared with individuals in the general population, which could have provided some interesting insights. A part of traffic accident statistics is based on mileage.

CONCLUSION

The results show that people with MD are at a lower risk of traffic accidents compared with individuals in the general population, which could be a result of selective driving. Despite the low accident rates reported in this study, it is important for individuals with MD to discuss their driving with their physician and seek necessary advice. Some individuals with MD, for instance, those who also suffer VDA leading to falls, and especially those with a history of transient loss of consciousness should abandon their driving until the situation has been brought under control with proper therapy and is consistently monitored.

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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Conflict of Interest: The authors have no conflict of interest to declare.

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