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Diverse phenotype of Ménière's disease associated with family history, thyroid disorder, migraine and associated disorders

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ABSTRACT

Objective: To better understand the clinical phenotype of Ménière's disease (MD), we examined family history, thyroid disorder, migraine, and associated disorders in complaints of people living with MD.
Method: We designed the study as a retrospective and examined data gathered from 912 participants with MD. Their data were originally collected by the Finnish Ménière Federation (FMF). The survey data included individual case histories for environmental factors, comorbidities, disease-specific complaints, impact-related questions, cognitive complaints, health-related quality of life (HRQoL), and sense of coherence (SOC).
Results: We observed significant differences between those with and without sporadic occurrence, family history, thyroid disorder, and migraine-associated complaints. Family history explained 20% of variability in patient complaints. Patients with a family history of MD whose disease started at younger age experienced balance problems, more severe vertigo spells, more severe vestibular drop attacks (VDA), and less nausea, although they had good SOC. Thyroid disorder explained 14% of variability in patient complaints. MD patients with a thyroid disorder comorbidity suffered more often from constant dizziness, balance problems, greater impact of hearing problems, cognitive complaints, and poor HRQoL. Migraine explained 12% of variability in patients' complaints and was associated with poor SOC and cognitive balance problems. MD patients with both thyroid disorder and migraine used antidepressants more often than other groups. Logistic regression analysis showed comorbidities of ischemic brain disorder (among 7.1%), kidney insufficiency (among 1.2%), and diabetes (among 7.3%) had statistically significant but restricted association with balance and gait problems, VDA, and reduced HRQoL.
Conclusions: Family history of MD and thyroid disorder or migraine comorbidities in MD influence the complaint pattern and partially explain complex symptom profiles, including symptoms of cognitive problems. Confounders play a minimal role in complaint profile and impact of MD whereas comorbidities influence the complaint structure and partly explain the complex symptom profile in MD.

1. Introduction

Ménière's disease (MD) can be characterized by episodic vertigo, fluctuating hearing loss, tinnitus, and aural fullness (Basura et al., 2020); however, as no objective methods exist for diagnosis, the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) suggests the use of symptom-based guidelines (Lopez-et al., 2015) for diagnosis of MD. Though the etiology

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of the disease is unknown, MD is believed to originate in the inner ear, and histological preparations or MRI can diagnose endolymphatic hydrops (Nakashima et al., 2016). MD is a chronic illness with a prevalence in the general population ranging between 0.27 and 0.5% (Havia et al., 2005; Tyrrell et al., 2014). The course of the condition is unpredictable and is associated with severe-to-profound hearing loss, vestibular drop attacks (VDA) with vertigo, balance and gait problems, poor health related quality of life (HRQoL), as well as functional limitations and restrictions (Pyykkő et al., 2016; Pyykkö et al., 2019, 2021). Although less frequently observed in MD research studies, the symptom of vestibular hypofunction can lead to cognitive problems of affected visuospatial abilities, processing speed, short-term memory, and executive function, and it can result in a heterogeneous complaint profile (Gürkov et al., 2019).

The reason for variability in complaints is not well understood, although it is reasonable to assume that variability may be associated with different genotypes, comorbidities, and confounders (Tyrrell et al., 2014; Frejo et al., 2017). Among several studies that have indicated an association of thyroid dysfunction (Brenner et al., 2004; Lin et al., 2019; Kim et al., 2020; Teggi et al., 2020), Kim et al. (2020) reported that thyroid diseases of goiter, hypothyroidism, and hyperthyroidism were all associated with MD, irrespective of the thyroid hormone level, and regarded this association as a sign of autoimmunity. In another study, 38% of patients with MD presented with significantly higher thyroid autoantibodies than the control group (Fattori et al., 2008). These studies suggest a predisposition of MD patients for thyroid disease, although its association with phenotype of MD has not been fully explored. There is evidence that various autoimmune diseases are associated with MD (Frejo et al., 2016), and this association can be determined with inflammatory markers in MD (Zou, 2019; Zou et al., 2023; Frejo et al., 2022).

Migraine is overrepresented among MD patients (Radtke et al., 2002) and has been hypothesized to share etiology with MD (Tabet and Saliba, 2017). The close association between migraine and MD has been recently classified as vestibular migraine (VM) (Lempert et al., 2012). VM patients may also show endolymphatic hydrops in MRI (Nakada et al., 2014). Family history is often positive for VM and MD (Frejo et al., 2016). Patients with MD or VM seems to have a different pro-inflammatory signature that may be used in differentiating VM from MD with migraine (Flook et al., 2019). The inadequate scientific differentiation between VM and MD has raised critics, as migraine may only aggravate the phenotype of MD as a comorbidity (Pyykkö et al., 2020). So far, it has been reported that the comorbidity with migraine would lead to more severe vertigo spells in MD.

Several candidate genes have been identified in MD, but genetic analysis provides little information on the etiology of sporadic MD. Most MD patients with family history seem to have autosomal dominant inheritance pattern with 60% penetrance (Parra-Perez et al., 2023) and a more severe phenotype. In a recent study, 15 genes have been reported in familial MD in the European population, and a novel hypothesis is supported (Frejo et al., 2023) which involves proteins in the attachment of stereocilia to the tectorial membrane for familial MD where multiple families share the same mutations for the genes OTOG, TECTA, and MYO7A. The complaint profile may vary by genetically different spectra of clinical subtypes. Previous studies have not reported differences in MD phenotype among patients with and without family history, although one study (Morrison et al., 2009) indicated more severe nausea, more intense vertigo attacks, and longer-lasting attacks than in sporadic cases. In another study (Hietikko et al., 2014), earlier onset and longer spells of vertigo were reported in MD patients with family history compared to patients with sporadic MD.

The aim of the present study was to examine complaint profiles in MD patients with special reference to comorbidities of family history, thyroid disorder, and migraine. Understanding the variability of MD would allow characterization of the disease into different disease subgroups, and this could further our understanding of underlying pathophysiologic mechanisms. It may also help improve our understanding of the physiology of the inner ear microenvironment and develop individual specific treatment strategies.

2. Method

2.1. Study design

This study was approved by the Ethical Committee of the Union of Finnish Ménière Association (Protocol no: 2022-06-08). The researchers used a retrospective design and analyzed anonymous registry data of MD patients collected from the Finnish Ménière Federation (FMF). Study participants completed informed consent before responding to the survey.

2.2. Participants

Data were collected from 962 of the 1200 FMF members who responded to a questionnaire conducted between 2012 and 2015. Among those 962 members, essential information was missing in 50, which resulted in a viable sample of 912 MD patients. The mean age of the participants was 60.2 years (range 25–80 years, SD = 12.1 years). The average duration of the disease was 12.6 years (range 0.5–50 years, SD = 11.2 years). Participants included 663 females (i.e., 78.7%) and 180 males (i.e., 21.3%); this was respective of gender distribution by the FMF as well as the prevalence of MD in Finland (Havia et al., 2005). The diagnosis of MD was confirmed based on symptoms using a computerized inference engine using the AAO-HNS diagnostic criteria (Rasku et al., 2015).

2.3. Data collection

The data was gathered using an extensive questionnaire with mixture of open-ended and structured questions that examined disease specific as well as impact of the disease on activity limitations and participation restrictions (see Appendix 1). An 86-item oto-neurology questionnaire was used for assessing the MD. The HRQoL was evaluated using the EuroQoL EQ-5D-3L questionnaire (Dolan et al., 1995). To evaluate the attitude toward illness or salutogenesis (i.e., the means of helping oneself through the difficulties of life measure), the short sense of coherence (SOC) questionnaire was applied (Antonovsky, 1993). It consists of cognitive component, manageability component and meaningfulness component. Further the SOC scores 35–60 points represented weak SOC, 61–75 moderate, and 76–91 strong SOC. Fatigue and anxiety were evaluated by questions adapted from 15D HRQoL scale (Sintonen, 2001). Complaint-specific problems were assessed by asking the participants to rate severity and frequency of the complaints and their impacts on a five-point Likert scale, ranging from *none* to *very severe*. Vertigo attacks and vestibular drop attacks (VDA) were assessed by frequency, severity, and associated factors (i.e., environmental pressure changes, physical strain) and how much impact they caused. Questionnaire items also asked about postural stability outside the attacks, problems with gait and impairment of motility, and impact of balance problems. Participants also self-reported about impacts of tinnitus, hearing loss, and hyperacusis. Comorbidities and other parallel disorders, including cognitive impairment, were addressed. Family history was assessed by questions about complaints in first-degree relatives, siblings, and children of periodic vertigo and hearing loss indicating MD. Since not all participants could recall their parents' or siblings' disease or diagnosis, this question also contained an option to respond *not known*. Some of the questions were voluntary, though most were mandatory.

2.4. Data analysis

The researchers analyzed the data using multiple correspondence

analysis. Where necessary, missing data were imputed. Logistic regression was used to examine factors influencing the complaint profiles in MD patients. In this analysis, the researchers created separate models for family history, thyroid disorder, and migraine as dependent variables. Kruskal-Wallis H-tests were used to examine differences between patient groups for various demographic and complaint variables (i.e., sporadic occurrence, family history, thyroid disorder, and migraine). Furthermore, group comparisons were made using the Mann-Whitney *U* test. As this was an exploratory study, a *p*-value of 0.05 was used for interpretation of statistical significance.

3. Results

3.1. Association of parallel disorders with MD

We collected data on various diseases associated with health care and aging such as hypertension, kidney disorders, head trauma, neck trauma, meningitis, diabetes, headache, migraine, ischemic heart disease, brain ischemia, atherosclerosis, and thyroid disorders. Supplementary data (see Supplementary Table 1) shows the association of these complaints with MD. Only kidney problems showed a different phenotype profile, but the number of subjects were very few in this group. In a logistic regression analysis, ischemic brain disorder (among 7.1%), kidney insufficiency (among 1.2%), and diabetes (among 7.3%) had statistically significant but restricted association with balance and gait problems, VDA, and reduced HRQoL. A detailed description of the influence of associated disorders on MD is provided in Appendix 2.

3.2. Inheritance associated with MD

3.2.1. Parent/s with vertigo

208 patients out of 678 (i.e., 30.7%) indicated their parent had experienced episodic vertigo or diagnosed MD, while 234 patients (i.e., 34.5%) were not certain whether a parent had any of these complaints. In a logistic regression analysis, family history explained 15.1% of the variability of complaints (Chi-square = 72.24, $p < .001$). MD patients with parent's illness in their background had earlier onset of MD, greater tendency to fall, more common episodic vertigo, less nausea, and poor HRQoL but good SOC (see Table 1).

3.2.2. Sibling/s with vertigo

In 149 patients out of 765 (19.5%), a sibling had vertigo and/or balance problems. In 147 of those patients (i.e., 19.2%), the sibling's symptom profile was not known or non-defined. In a logistic regression analysis, sibling family history trend explained 15.7% of the variability of complaints (Chi-square = 74.70, $p < .001$). MD patients who had siblings with MD experienced greater tendency to fall, more common episodic vertigo, less nausea, environmental pressure-provoked spells, problems with balance when rising from chair, problems speaking during spells, and impact of cognitive complaints associated with MD. However, they had good SOC (see Table 1).

3.2.3. Both parent/s and sibling/s with vertigo

79 patients (10.2%) out of 912 subjects reported that both a parent and a sibling had vertigo. Family history could explain 11.1% of the variability of complaints (Chi-square = 39.89, $p < .001$). MD patients with family history of MD in both a parent and a sibling had more gait problems, greater tendency to fall, greater physical strain-induced vertigo, and good SOC (see Table 1). We found 17 families in whom a parent, a sibling, and a child of the patient also had MD.

3.2.4. Either parent/s or sibling/s with vertigo

278 patients (33.6%) out of 827 patients reported that either their parent or sibling had suffered from vertigo. In a logistic regression analysis, the family history trend explained 19.6% of the variability of complaints (Chi-square = 118.91, $p < .001$). MD patients with family history of MD in either parents or siblings had MD occurrence at an earlier age, greater tendency to fall, more frequent episodic vertigo, more environmental pressure-provoked spells, and numbness of the face but less nausea and good SOC (see Table 1).

Table 1
Outcome of logistic regression analysis in subjects with MD with family history, thyroid disorder, and migraine as dependent variables.

Models	Dependent Variables	Negelkerke Square	Variable Contributing to the Model
Family history	Parent's vertigo	0.15	Younger age of MD onset, Tendency to fall, Episodic vertigo, Less nausea, Good SOC, Reduces HRQoL
	Sibling's vertigo	0.16	Tendency to fall, Episodic vertigo, Less nausea, Problems in environmental pressure variation, Problems when rising from chair, Good SOC, Speech problems during spells, Impact of vertigo attacks
	Either parent's or sibling's vertigo	0.2	Younger age of onset of MD, Tendency to fall, Episodic vertigo, Less nausea, Problems in environmental pressure variation, Numbness of the face, Good SOC
	Both parent's and sibling's vertigo	0.11	Tendency to fall, Physical strain provoked vertigo, Gait problems, Good SOC
Thyroid disorder	Thyroid disorder	0.14	Younger age of MD onset, Constant dizziness, Environmental pressure provoking vertigo, Feeling of drunkenness, Feeling of light-headedness, Speech problems during spells, Reduced HRQoL, Impact of hearing problem
Migraine	Migraine	0.12	Feeling of floating, Reduced SOC, Impact of headache, Numbness of the face

Note: HRQoL - general health related quality of life measured using the EQ-5D-3L instrument; SOC= Sense of coherence.

3.3. Association of thyroid disorders with MD

One hundred and thirty out of 885 patients (14.7%) had problems with thyroid function, either under replacement therapy after thyroidectomy or thyroid malfunction. In a logistic regression analysis, thyroid disorder could explain 11.8% of the variability of complaints (Chi-square = 59.24, $p < .001$). MD patients with associated thyroid disorder had earlier onset of MD, constant dizziness, environmental pressure-provoked vertigo attacks, greater impact of hearing loss, and cognitive complaints such as lightheadedness, drunkenness, speech problems during vertigo spells, and reduced HRQoL (see Table 1).

3.4. Association of migraine with MD

Of the 886 patients with MD, 197 (22.2%) had migraine. In a logistic regression analysis, 11.5% of the variability in complaints could be explained by migraine (Chi-square = 65.84, $p < .001$). MD patients with associated migraine had lower SOC, impact of headache, and cognitive complaints such as floating-type balance problems and numbness of face (see Table 1).

3.5. Differences in complaints based on sporadic occurrence, family history, thyroid disorder and migraine

In this analysis, we excluded cases who had overlapping occurrences of family history and comorbidities of thyroid disorder and migraine

(see Table 2), resulting in 827 patients for the analysis. The patients with migraine were younger than others (Anova F = 3.6, p = 0.013). In addition, the duration of MD in the migraine group was shorter than others (Anova F = 5.4, p = 0.001). Table 3 presents the results of qualitative data analysis for differences in complaints across MD patient groups.

3.5.1. Vertigo types

Fig. 1 illustrates the current vertigo types across MD patient groups based on sporadic occurrences, family history, thyroid, and migraine. The groups differed in vertigo complaint significantly (Kruskal-Wallis test H = 48.862, $p < .001$). Vertigo in sporadic and migraine groups progressed from episodic to constant dizziness more often. MD patients with *thyroid disorder* (Mann-Whitney test, $p < .001$) and *family history* ($p = .004$) had more frequent episodic vertigo than the sporadic MD group. Also, MD patients in these two groups had less frequent dizziness than the sporadic MD group ($p < .001$) The patients with *migraine* had episodic vertigo less commonly than the sporadic MD group ($p = .047$). For the duration of episodic vertigo and frequency of spells, there was no difference between the four groups. Also, MD patients with family history had significantly less nausea than other groups (Kruskal-Wallis test H = 9.509, $p = .022$).

Impact of Vertigo. We evaluated the impact of vertigo spells across participant groups and found statistically significant differences between the groups (Kruskal-Wallis test, H = 8.9, $p = .031$). In pairwise comparison, the impact of vertigo was more severe among patients with *migraine* ($p = .007$) and those with *thyroid disorder* ($p = .027$) than the baseline *sporadic* occurrence group and those with *family history* (see Table 3). However, the intensity of individual vertigo spells was more disturbing in the family history and thyroid-associated groups (see Supplementary Fig. 1 in Appendix 2). No differences were observed in frequency or duration of vertigo spells among the different groups (see Supplementary Figs. 2 and 3 in Appendix 2).

3.5.2. Balance problems

There was a difference between patient groups in terms of balance problems, i.e., postural stability (Kruskal-Wallis test H = 9.6, $p = .022$), as illustrated in Table 3. In pairwise comparison, balance problems were more severe among patients with *migraine* ($p = .01$) and *thyroid disorder* ($p = .029$) compared to the baseline *sporadic* occurrence group and those with *family history*.

3.5.3. Severity of vestibular drop attacks

Severity of VDA varied between the groups, as illustrated in Table 3 (Kruskal-Wallis test H = 11, $p = .012$). In pairwise comparison, VDA was more frequent among patients with *migraine* ($p = .002$) and *thyroid disorder* ($p = .014$) than in the baseline *sporadic* occurrence group and those with *family history*.

Table 2
Number of MD patients having only family history, thyroid disorder, or migraine.

	N (%)	Mean age ± std years	Duration of MD ± std years	Mean onset of MD ± std, years
Sporadic occurrence	373 (45.1%)	61.1 ± 12.3	15.4 ± 11.9	44.2 ± 13.17
Family history	262 (30.5%)	60.3 ± 11.9	18.7 ± 11.6	41.5 ± 12.1
Thyroid disorder	91 (11.0%)	65.4 ± 12.4	16.5 ± 13.8	46.8 ± 14.2
Migraine	111 (13.4%)	54.5 ± 16.7	14.0 ± 11.0	41.5 ± 12.1
Total	827 (100%)	60.1 ± 12.6	16.3 ± 12.0	43.5 ± 12.9

Table 3
Difference in complaints across MD patient groups.

Complaints	Sporadic	Family history	Thyroid disorder	Migraine	Kruskal-Wallis H/ ANOVA test
Impact of vertigo	1.48 +-1.06	1.46 +-1.03	1.79 +-1.03*	1.79 +-1.16*	H = 13.1 p = .094
Impact of gait problems	0.86 +-1.0	1.01 +-1.03	1.13 +-1.16*	1.05 +-0.99*	H = 8.6 p = .035
Severity of VDA	1.44 +-1.27	1.41 +-1.27	1.75 +-1.40*	1.87 +-1.44*	H = 12.4 p = .006
Anxiety	1.35 ± 1.16	1.40 ± 1.12	1.59 ± 1.08	1.63 ± 1.05*	H = 8.29 p = .040
Energy	1.23 ± 0.96	1.06 ± 0.88	1.45 ± 0.97*	1.50 ± 0.95**	H = 20.3 p = .001
SOC	62.58 ± 16.48	69.54 ± 12.93*	63.01 ± 14.38	56.59 ± 16.42*	F = 17.8 p < .001
HRQoL	0.76 ± 0.19	0.72 ± 0.20	0.67 ± 0.18*	0.70 ± 0.18*	F = 7.2 p < .001
Use of anti-depressive medication (%)	21%	21%	38%*	034%*	H = 17.5 p = .001

Note: Complaints are classified in 5-point scale. Drug usage as percentage of users. Mean and SD are shown. Stars indicate statistical difference between groups when compared to sporadic occurrence group.

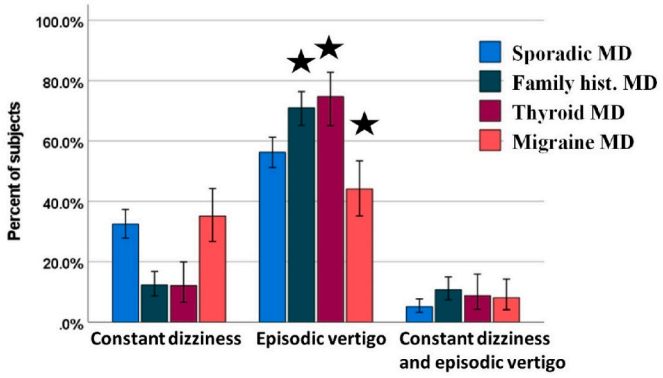

Fig. 1. Vertigo Types Across MD Patient Groups Based on Sporadic Occurrence, Family History, Thyroid Disorder, and Migraine. *Note:* Mean and SE are shown. Stars indicate statistical difference between groups when compared to sporadic occurrence group.

3.5.4. Energy

Regarding loss of energy (chronic fatigue), we observed significant differences between the groups (Kruskal-Wallis test H = 17.2, $p = 001$). In pairwise comparison using the Mann-Whitney test, chronic fatigue was more severe among patients with *thyroid disorders* ($p = .008$) and *migraine* ($p = .003$) compared to *sporadic* and *family* history groups.

3.5.5. Sense of coherence

As shown in Table 3, a statistically significant difference in SOC was observed among the groups (Kruskal-Wallis test H = 8.9, $p = .031$), indicating that patient attitude toward illness and ability to cope with MD differed between the groups. In a pairwise comparison, patients with *family history* had moderate SOC, indicating people in that group were somewhat less vulnerable in their attitudes toward the disease than in *sporadic* cases ($p < .001$). Patients with *migraine* had weak SOC ($p < .001$) when compared to the baseline *sporadic* occurrence group, although no significant difference was observed for the *thyroid* group.

3.5.6. Health-related quality of life

HRQoL significantly varied between groups (Kruskal-Wallis test H = 22.9, $p < .001$), as illustrated in Table 3. In pairwise comparison,

reduction of HRQoL was observed among patients with *thyroid disorders* ($p < .001$) and with *migraine* ($p < .001$) when compared with the baseline *sporadic* group and those with *family history*.

3.5.7. Drug usage

We collected data about patient's use of alcohol, diuretics, gentamicin therapy, analgesics, and antidepressants and found MD patients with *sporadic* occurrences and *family history* used alcohol more frequently than those with *thyroid* disorder or *migraine* (Kruskal-Wallis test H = 13.8, $p = .003$). Of the 834 patients, 458 used diuretics, and 27 were treated with gentamicin. We did not observe any difference in the outcome of diuretic treatment or gentamicin therapy among different comorbidity categories (Kruskal-Wallis test, H = 2.803, $p = .413$, H = 2.132, p = 0.546). We observed MD patients with *migraine* used NSAID analgesics more frequently (Kruskal-Wallis test H = 28.4, $p < .001$). Further, patients with *thyroid disorder* (45 out of 151) and *migraine* (38 out of 72) used antidepressants more frequently than the *sporadic* group (Kruskal-Wallis test H = 15.515, $p = .001$). Regarding anxiety medications, we observed that only the *migraine* group differed significantly from the *sporadic* group (see Supplementary Fig. 4 in Appendix 2).

3.5.8. Hearing loss

Audiograms were available in 156 subjects with MD. Analysis of the worst-hearing ear in those audiograms showed that on average, hearing began to deteriorate permanently after the first year of onset of MD (with audiometrically confirmed hearing loss) and continued to deteriorate to 40 years of age.

Of the 912 subjects with MD, 237 subjects (26.0%) reported bilateral hearing loss and were interpreted to have bilateral MD. Analysis showed no significant differences between unilaterality and bilaterality of MD between the phenotype groups (Kruskal-Wallis test, H = 1.635, p = 0.652). These results indicate that neither family history, thyroid, or migraine-associated MD necessarily progresses to bilateral MD.

We also analyzed the onset of MD, as some authors have used this phenotype classification for patients with MD who have hearing loss as a first symptom, or "delayed hydrops MD" (Lopez-et al., 2017). One hundred and forty nine patients reported having hearing loss as a first symptom, but we did not find any significant differences around this phenotype between the comorbidity groups (Kruskal-Wallis test, H = 1.10, p = 0.778).

4. Discussion

The aim of the present study was to evaluate phenotype variation of MD in patients with and without family history, thyroid disorder, or migraine. We observed differences in complaints profiles among the different MD-comorbidity groups, and we found complaints referable as cognitive disorders were also common in these patient groups. These complaint characteristics could partly explain variability in complaint profiles of MD patients. Our results suggest that focusing only on key elements of MD such as vertigo spells, hearing loss, and tinnitus may not be sufficient during management planning. Interestingly, we also analyzed whether bilateral hearing loss would be different among the study groups, but we could not show any statistically significant differences in proportion of bilaterality between the phenotype groups (see Appendix 1).

4.1. Family history and MD

Our findings highlighted that family history could explain about 20% of variability in the phenotype. We evaluated parents, siblings, and children separately and found both dominant and recessive inheritance. We found 17 families in whom all three generations were disabled with MD, which could be interpreted as dominant inheritance. As the data were anonymous, we were unable to determine the exact rules of inheritance. MD patients with family history of MD had more severe impacts on mobility and balance, more frequent periodic attacks of vertigo, and earlier onset of MD. Despite more frequent periodic vertigo, they had relatively good HRQoL and SOC, indicating their good ability to cope with MD.

It has been suggested that phenotypic variation in MD results from multiple individual genes (Phillips et al., 2018). More than 15 genes have been reported in familial MD in the European population, and a novel hypothesis (Parra-Perez et al., 2023) indicated that for familial MD, proteins are involved in the attachment of stereocilia to the tectorial membrane. In sporadic MD, the current focus is directed to immune system activating genes (Zou et al., 2023; Frejo et al., 2023). A study by Galleo-Martinez et al. (Gallego et al., 2019) reported a burden of rare variation in certain hearing loss genes in sporadic MD, which might have an additive effect on MD phenotype. An association with autoimmunity and hereditary of MD has also been reported when comparing sporadic occurrences and family history groups (Hietikko et al., 2014). Additionally, the genetics of immune signaling pathways has been studied in MD, but no specific immune pattern has been found (Zou et al., 2023; Frejo et al., 2022; Flook et al., 2019). Further studies must clarify phenotype variation and their dependence on specific genetic linkage.

4.2. Thyroid disorders and MD

Thyroid disorders explained 14% of variability in complaints of MD patients. Also, we observed that MD subjects with thyroid problems had more frequent episodic vertigo and suffered from greater impact of vertigo. The phenotype was also characterized by poor HRQoL, chronic fatigue, and other cognitive complaints. Those with thyroid disorders also used antidepressants more frequently. In Finland, thyroid disorders are present in 4–5% of the population (National Institute for Health and Welfare, 2000); however, the rate in MD associated with thyroid disorders is 14.7%, which far exceeds the population rate.

Previous studies have suggested the association of hypothyroidism with MD (Brenner et al., 2004). Lin et al. (2019) demonstrated a significant association between hypothyroidism and MD, especially in elderly female patients. These authors asserted thyroxin deficiency could be prevented by replacement therapy. To delineate the association of various thyroid diseases with MD, Kim et al. (2020) identified 8183 adult patients with MD and matched them with 32,732 referents. The histories of goiter (5.7% vs. 4.2%), hypothyroidism (4.7% vs. 3.6%), thyroiditis (2.1% vs. 1.6%), hyperthyroidism (3.6% vs. 2.5%), and autoimmune thyroiditis (0.99% vs. 0.67%) were significantly higher in the MD group than in the referents. Kim et al. (2020) could not demonstrate in detailed analysis that thyroxin level or replacement therapy in hypo- or hyperthyroidism would be independently associated with MD. However, Lin et al. (2019) suggested physicians should consider verifying thyroid function and history of thyroid diseases when encountering patients with MD. Supporting the autoimmunity theory, Zou et al. (2023) indicated comorbidity of MD and hypothyroidism secondary to hyperthyroidism was associated by next-generation sequencing of the immune genome. It should be acknowledged that thyroid complex is only one signature of autoimmunity in MD, and there are other autoimmune diseases that seem to collaborate with MD (Lopez et al., 2023).

4.3. Migraine and MD

Prevalence of migraine has been reported to be twice as high in a group of patients with MD than in an age- and sex-matched control group (Teggi et al., 2020). In the present study, migraine was diagnosed in 22.2% of the participants, exceeding the 10% reported in general population (National Institute for Health and Welfare, 2000). The high prevalence of migraine may result in a high proportion of females in the study material, as migraine is more prevalent in females. We tried to exclude patients with VM in a previous study but could not confirm the diagnosis of VM among the subjects (Pyykkö et al., 2019) and used the

terminology *MD with migraine*. One of the problems with previous literature is that most papers describing VM were published before definite criteria for VM had been established (Lempert et al., 2012) and are therefore controversial in current work. It has been suggested that VM and MD have a common mechanism that leads to similar inner ear symptoms. The diagnostic criteria for VM were the product of an accord between the classification committees of the IHS and the Bárány Society (Lempert et al., 2012), whereas there is still a concern in the scientific community about the relevance of VM as an independent disorder from MD rather than as a comorbidity (Pyykkö et al., 2019).

In a review, Tabert and Saliba (Tabet and Saliba, 2017) evaluated the complex association of migraine with MD and sought to classify the characteristics of VM. Unfortunately, there was much overlap regarding symptomatology for MD with migraine and WM, and this created diagnostic uncertainty. For example, Neff et al. (2012) demonstrated that none of the signs, symptoms, or investigations could distinguish MD and VM from each other. Neff et al. (2012) concluded that more specific diagnostic criteria are needed to differentiate these diseases and address their coexistence. So far, both MD and VM are using exclusion criteria of other diagnoses to assess the current diagnosis. To be clear, these criteria exclude each other. So far there are a limited number of studies in which the separation between MD and VM are based on statistical workups, as most studies either describe the co-association of migraine with vertigo or vertigo with migraine (Tabet and Saliba, 2017).

As of this study, we consider it safe that migraine is treated and analyzed separately from MD, although these are undoubtedly associated. Comorbidity with migraine explained 12% of the variability of phenotype of MD. When compared with the sporadic MD occurrence group, those with migraine differed and showed poor SOC, more frequent constant dizziness, greater impact of vertigo, more frequent attacks of VDA, more severe gait problems, and different cognitive complaints. They also used antidepressants more frequently.

4.4. Note on methods used in searching for differences in phenotyping

Recently, outcomes of cluster analysis of MD phenotypes have been published (Lopez-et al., 2017; Crossley et al., 2020) considering four different clusters (autoimmune, familial, migraine associated, and delayed MD). Two-step cluster analysis is a statistical method that clusters data points based on their similarity. It applies unsupervised learning, as it does not require any prior knowledge of the data or the number of clusters to be found. The aim of clustering was to tailor and search for optimal therapeutic possibilities for different phenotype variants in MD. So far, no therapeutic solutions have been presented.

In the present study, we attempted two-step cluster analysis, and we could partly confirm the outcome of the cluster analysis but could not ascertain the validity of this method at different complaint levels. For example, patients with a history of hearing loss before the onset of vertigo episodes were clustered by Lopez-Escamez (Lopez-et al., 2017) as delayed MD. In the present study, we identified 149 patients (16.3%) with hearing loss as a first symptom (before vertigo), whereas bilateral MD studies (Frejo et al., 2016) did not deal with the “delayed hydrops group” but used asynchronous hearing loss as its own category. One reason for differences between our study and the previous studies may be that the results of two-step cluster analysis can be difficult to interpret, and it can be difficult to determine what the clusters represent. It is also important to use a variety of methods to assess the quality of the clustering results. In our two-step cluster analysis, the quality of determination of clusters was poor and may depend on outliers. Two-step cluster analysis is sensitive to the choice of distance metric, linkage method, and outliers, which can distort the clustering results. Thus, further studies and other common methods, for example, silhouette analysis and Calinski-Harabasz, should be included in the analysis.

4.5. Cognitive aspects in MD complaints

Some patients present with vestibular ailment complaints using expressions that are difficult to classify in strict medical terms. MD patients with thyroid problems and migraine, especially, had cognitive problems. These included constant dizziness, chronic fatigue, drunkenness and lightheadedness, brain fog, poor anticipation of movements, and emotional or psychological avoidance reactions. Dizziness and balance problems may include vestibular ailments related to MD like the recently introduced *persistent postural perceptual dizziness* (PPPD), fear of falling, or Mal de debarquement syndrome (MdDS), among others (Pyykkö et al., 2021; Staab et al., 2017; Dai et al., 2014).

PPPD manifests with one or more symptoms of dizziness, unsteadiness, or non-spinning vertigo that are present on most days for at least three months or more and are exacerbated by upright posture, active or passive movement, and exposure to moving or complex visual stimuli (Staab et al., 2017). Emerging research suggests PPPD may arise from functional changes in postural control mechanisms, multi-sensory information processing, or cortical integration of spatial orientation and is associated with psychopathological and cognitive consequences. MdDS consists of rocking or swaying balance problems arising either spontaneously or associated with vestibular disease (Chari et al., 2021) and is suggested to be produced due to a conflict within a single sensory system (e.g., canal-otolith interaction) or in the interaction between two or more sensory systems (e.g., visual and vestibular systems) (Nachum et al., 2004). The Bárány Society definition suggests MD is a broader concept than defined by episodic vestibular ailment but does not provide an explanation of dizziness by discrediting constant vertigo as a crucial factor in MD (Lopez-et al., 2015). The present study also shows that cognitive complaints are an essential part of MD, although in different societies, it may be classified under different disease umbrellas.

Chari et al. (2021) tried to explore the content of the Dizziness Handicap Inventory (DHI) to understand the cognitive impairment included in this questionnaire and noticed high prevalence of cognitive symptoms in patients with episodic vestibular disorders. According to Dieterich and Staab (2017), the neurophysiological explanation indicates maladaptation of the cognitive system associated with the vestibular system, which results in altered activation in different parts of the brain. Thus, for example, *tendency to fall* describes balance problems but also contains significant cognitive content (Rizk et al., 2020). Chari et al. (2021) concluded alternative methods must be used to identify vestibulopathic patients with cognitive symptoms to initiate strategies for prevention and treatment. To avoid medicalization of the patient history, we tried to develop a questionnaire on complaints that would be patient-oriented. A patient-oriented complaint profile may help to enhance focus on individual needs for rehabilitation with cognitive therapy and peer support.

4.6. Limitations of the study

In Finnish, the word for *vertigo* indicates dizziness, balance problems, and vertigo, among others. Therefore, we attempted to characterize the type of vestibular complaint with specific questions and to differentiate between the terms *vertigo* (rotatory attacks with spinning sensation) and *dizziness*. We found the Finnish words for *vertigo* and *dizziness* were often misinterpreted as balance and gait problems, cognitive complaints, and light-headedness. The misunderstanding of patient-oriented terminology may bias the outcome of the results, and all complaints might be covered under umbrella of dizziness.

As the current study is based on self-reports, there are several limitations. The questionnaire was anonymous, and we could not make focused supplementary questions for the participants or to retrieve retrospective hospital reports. For these reasons, the current study results should be interpreted with caution and should be treated as exploratory.

We had extremely limited access to audiometry data (156 out of 912

subjects) that resulted in limitations with the logistic regression and two-step cluster analyses. However, we analyzed the *impact of hearing loss* in the study. This approach may bias outcome in patients with *fluctuant* hearing loss, who may consider their hearing as normal or contrary to audiometric data in periods of *sudden* hearing loss. As for the diagnosis of MD, several tests have been applied such as inner ear MRI, caloric tests, evoked vestibular evoked responses, and head impulse tests, among others. None of these tests are reliable to diagnose MD; therefore, diagnostic recommendations are based on complaint patterns and hearing tests. In future, if cytokine test panels can reliably diagnose MD (Zou et al., 2023) and discriminate between VM and MD (Flook et al., 2019), then use of molecular panels can explain phenotype variations more exactly than the statistical means in the present paper.

There was a predominance of female participation in this study; this may be related to the predominantly female membership of Finnish Meniere Federation (FMF), or it might be due to the tendency of more females to be more socially active in health care. There seems to be no difference, however, in the complaint profile related to gender, and our study's gender bias may not bias our statistical outcomes.

5. Conclusions

The current study showed that the phenotype of MD between those with and without family history, thyroid disorders, and migraine can partly be explained by patient complaint profiles. Moreover, the study highlighted that MD patient groups based on *sporadic occurrence, family history, thyroid disorder,* and *migraine* varied in terms of elements including type of vertigo, impact of vertigo, severity of VDA, balance problems, chronic fatigue, SOC, and HRQoL. Our results suggest examining MD patients solely in terms of key issues such as vertigo spells, hearing loss, and tinnitus may not be sufficient, and more detailed examination in terms of complaint profiles is needed during rehabilitation and management planning.

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Declaration of competing interest

None of the authors have conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joto.2024.07.005.

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