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Cardiovascular Risk profile in Ménière's Disease and Posterior Circulation Infarction: A Comparative Study

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Abstract: Ménière's disease (MD) has an unclear cause. The microvascular dysregulation of the inner ear has been increasingly pointed as a potential contributor. This study investigates the prevalence of cardiovascular risk factors (CVRFs) in MD patients compared to those with posterior circulation cerebral infarction (POCI). CVRFs like hypertension, diabetes, dyslipidemia, obesity, coronary heart disease, and smoking were assessed in both MD and POCI patients. Brain MRI identified POCI etiology as "small vessel occlusion" (SVO) or "other etiology" (OE). The study included 64 MD and 84 POCI patients. Compared to MD, POCI OE showed a higher prevalence of CVRFs across various age groups, including hypertension, diabetes, dyslipidemia, and smoking. Notably, the odds of having POCI OE were significantly higher for individuals with hypertension and smoking. On the other hand, POCI SVO showed similar prevalence of CVRFs compared to MD. This study reveals no significant difference in CVRF prevalence between MD and smaller vessel POCI. However, a clear distinction emerges when comparing MD to POCI with involvement of larger blood vessels. Further research is needed to confirm these findings and explore potential shared risk factors between POCI (SVO) and MD.

Keywords: Ménière´s disease; stroke; vertebrobasilar; cardiovascular; risk factors; microcirculation; inner ear; posterior circulation; POCI; cerebral

1. Introduction

Ménière's disease (MD) is a multifactorial inner ear disorder characterized by episodic vestibular symptoms, sensorineural hearing loss, tinnitus, and aural pressure [1]. Despite the increasing use of magnetic resonance imaging (MRI) and computed tomography (CT) scans, MD is diagnosed clinically [2].

Endolymphatic hydrops (EH) is a hallmark pathologic characteristic of MD, as described by Hallpike and Cairns [3,4]. While EH is observed in all MD patients, not all EH patients show MD symptoms (the so called “asymptomatic hydrops”) [3,5,6]. The observation of EH in temporal bones of asymptomatic individuals prompted the discussion on the true role of EH - as a mere ubiquitous finding of MD instead of a causal mechanism for MD symptoms [7]. EH is often evident in the cochlea as a distension of Reissner's membrane into the Scala vestibuli [8]. Other membrane structures in the ear, such as those enclosing the saccule, utricle, and semicircular canal ampullae, may also be displaced to variable degrees [9]. Membrane ruptures, herniations, and scarring have been found in certain specimens [10]. Those who defend a causal relationship between EH and MD point to membrane´s rupture as an important contributor for MD´s periodic attacks and functional alterations [3].

To date, it is unknown why certain individuals are more prone to develop EH. Similarly, it is uncertain which factors make EH more likely to translate into clinical MD [3]. An interaction between

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genetical and environmental factors has been proposed [11]. However, the findings of genetic research on MD are debated due to the complexity of MD´s pathophysiology. MD has been linked to a plea of different disorders such as inflammation, immunology, water and ion balance in endolymphatic fluid, viral infections, metabolism, and aberrant nerve conduction function [12].

It is clear that no unanimously accepted model explains the pathogenesis of MD [6,13]. However, a recent hypothesis of microvascular dysregulation of the inner ear has been explored [6,13]. Some speculate that impaired endolymphatic sac's blood flow and fluid balance as a result of vascular dysfunction may lead to endolymph buildup, resulting in vertigo bouts [14]. A decrease in blood flow to the inner ear caused by microvascular damage, oxidative stress, atherosclerotic plaque development or microthrombosis might disturb the balance of endolymphatic fluid production and absorption, raising the risk of EH and, eventually, MD [15–17]. On the other hand, EH constitutes itself a resistor to inner ear vascular perfusion [6]. In cases where EH is present, chronic vascular impairment of the inner ear may impose an additional irrigation challenge - resulting in lower ear perfusion pressures. This scenario of chronic ear ischemia may alter ion and fluid balance within the inner ear, favoring MD attacks [6]. An important study revealed important degenerative changes in the capillaries of the blood-labyrinthine barrier (BLB) in MD [18].

Small artery disease has been explicitly hypothesized to contribute to inner ear homeostasis instability and result in EH [6,13]. Clinical signs of inner ear´s chronic small vessel disease are hard to describe both clinically and on imaging [19,20]. It is known that the inner ear is irrigated by the labyrinthine artery coming from the vertebrobasilar arterial system [20]. In parallel, small-vessel strokes are a well described clinical and imagological subtype of vertebrobasilar (posterior circulation) vascular events. In case small-vessel irrigation of the inner ear could relate to MD physiopathology, MD patients could then share similar cardiovascular risk factors to posterior circulation infarction patients (POCI), namely the ones caused by small-vessel disease.

The inner ear and brainstem/posterior cerebral regions rely on a shared arterial irrigation. Nevertheless, to date, no studies compared cardiovascular risk factors (CVRF) between MD and POCI patients. With this in mind, this study compares the prevalence of CVRF in MD to a group of individuals with POCI.

2. Materials and Methods

In order to perform a retrospective study, a sample of patients with definitive diagnosis of MD from the Otorhinolaryngology consultation were compared with a sample of patients with POCI from the Neurology consultation. Brain MRIs were assessed by a member of the Neuroradiology Department (JT) and by a Neurologist (RR). Data acquisition was made between 2019 to 2023 using non-probability sampling. Figure 1 depicts the methodological approach.

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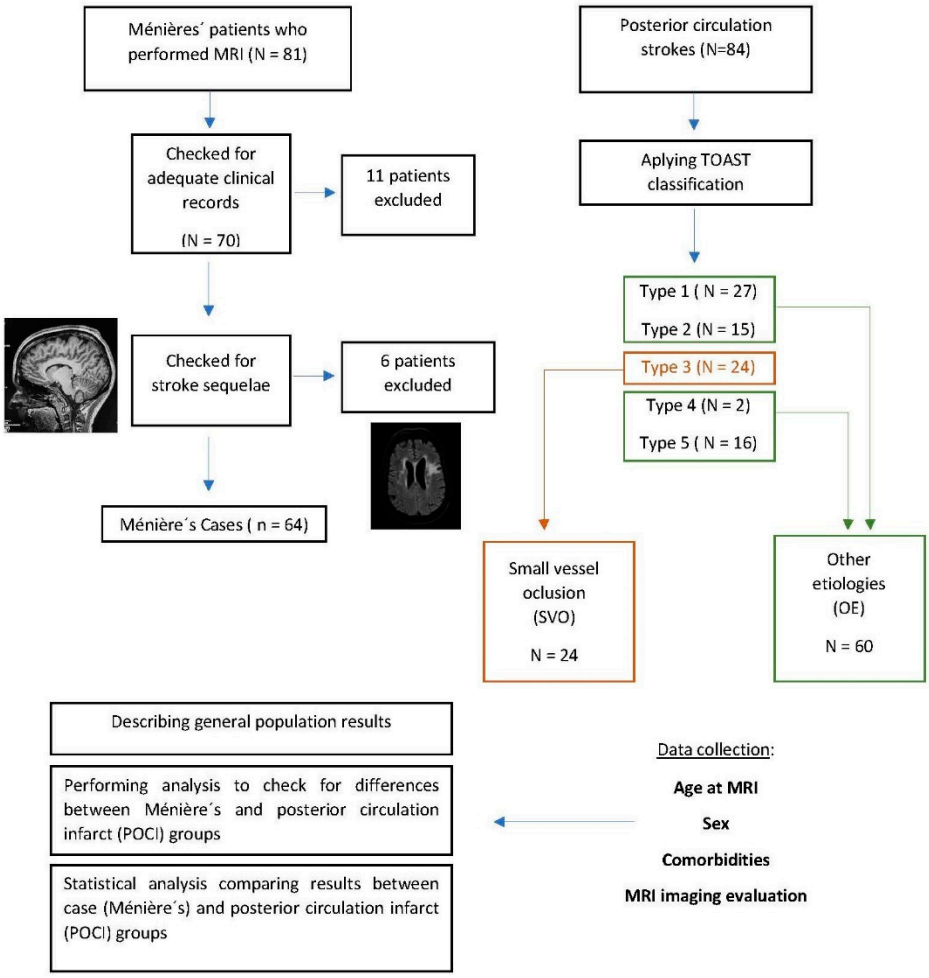

Figure 1. - Methodological approach flow chart.

Inclusion criteria for MD patients were: definite MD according to Bárany Society, EAONO , the AAO-HNS, the Japan Society for Equilibrium Research, and the Korean Balance Society [21]; age ≥ 18 years; available brain MRI; absence of other cochleovestibular lesions on MRI (namely facial or vestibular Schwannoma and cerebellopontine Meningioma), adequate clinical records. Exclusion criteria: evidence of any former stroke sequelae on MRI.

For POCI, inclusion criteria were: age > 18 years, brain MRI with anatomical localization of the lesion, absence of reported hearing or vestibular impairment prior to the event, adequate clinical records.

The following CVRFs were assessed based on existent hospital and primary practice records: hypertension, diabetes mellitus, dyslipidemia, obesity, heart disease and smoking. Hypertension was considered in any patient receiving pharmacological treatment specifically aimed at addressing elevated blood pressure. Diabetes mellitus was ascertained based on documented medical history or the use of antidiabetic medications. Dyslipidemia was defined by abnormal lipid panel results or documented use of lipid-lowering agents. Obesity was determined by body mass index (BMI) measurements, with values ≥ 30 indicating obesity as per established criteria. Heart disease encompassed a history of myocardial infarction, coronary artery disease, arrhythmias or other clinically documented cardiac conditions. Smoking status was determined by self-reporting or documentation of current or recent (within the last 12 months) smoking habits in medical records.

The etiology of POCI was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST). For analysis purposes, the sample was further divided into "small vessel occlusion" (SVO) - corresponding to the type 3 classification of TOAST and "other etiologies" (OE) - corresponding to Type 1,2,4 and 5 of the TOAST classification (see Figure 1 and Figure 2). Age categories were created to compare groups in order to minimize age bias on risk factors´ prevalence.

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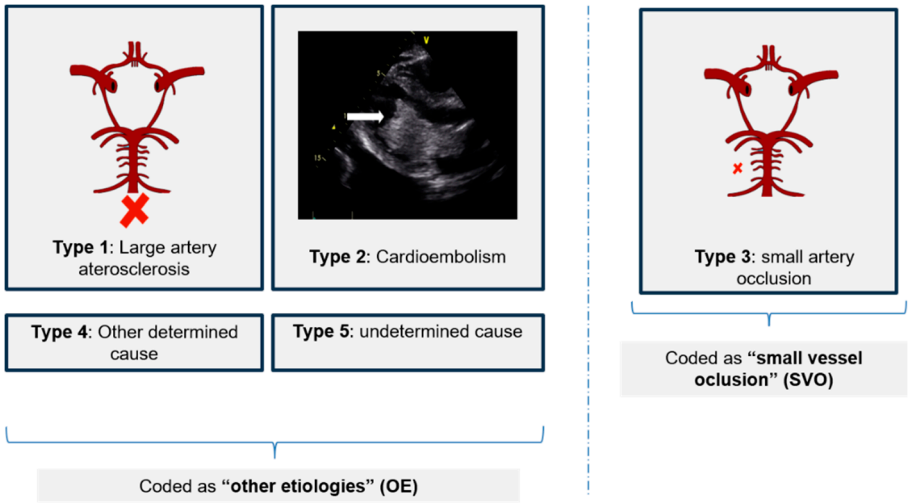

Figure 2. - Classification of posterior circulation infarction (POCI) according to the TOAST classification, and their subsequent division into 2 categories for analysis. Red cross mark: place of arterial occlusion (large vs small vessel); white arrow: intracardiac mass.

SPSS (IBM SPSS Statistics 29) was used for statistical analysis. Specific risk factors were coded as categorical variables and are hence reported as percentages in the descriptive analysis. Number of comorbidities in each subject were measured as an ordinal variable. Continuous variables such as age are shown as means and standard deviations. Skewness, kurtosis, and the Kolmogorov-Smirnov tests were used to ensure that the distribution was normal. The bivariate correlations were analyzed using Pearson´s chi-square test in the descriptive analysis and then inside each age category to compare the prevalence of each risk factor. A multinominal logistic regression (MLR) was employed to produce a predictive model adjusted for age, taking group (Ménière, POCI SVO or POCI OE) as the dependent variable and CVRF as covariates. MLR was preferred since the dependent outcome variable defined as "group" had 3 categories and was unordered. Additionally, proportional odds assumption proved violated in the test of Parallel lines. In the regression analysis, the decision not to include sex as an independent variable was based on the consideration of potential collider bias. All presented p-values are two-tailed, with a p-value ≤ 0.05 indicating statistical significance.

3. Results

3.1. Study Population

A total of 81 patients with MD were initially recruited, with 11 exclusions due to insufficient clinical data and 6 exclusions due to incidental cerebrovascular disease on MRI, making a total of 64 MD patients without signs of prior stroke. In parallel, a total of 84 POCI patients were included, accounting for the final 148 patients. Of those, 88 were men (56.1%) and 60 women (38.2%), with a mean age of 59 ± 14 years. Table 1 describes the sample´s characterization within and between groups. Figure 3 and Figure 4 are graphical representations of the sample distribution within age and sex categories, respectively. Figure 5 depicts in detail the group description within the sample.

Table 1. Descriptive and bivariate analysis of Ménière´s and posterior circulation infarction (POCI) groups concerning age and sex.

Continuous variables	Mean (± Standard deviation)		P-value	Categorical variables	Frequency (%)		P -value
	Ménière	POCI			Ménière	POCI	
				Age (categories)			
				< 45 years	18.8	14.3	0.465
				45-55 years	34.4	10.7	**<0.001**
Age (years) [1]	56.2± 12.9	61.7± 13.8	0.014	55-65 years	20.3	35.7	**0.041**
				65-75 years	17.2	20.2	0.639
				> 75 years	9.4	19	0.101

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	Sex (male)	40.6	73.8	**<0.001**

[1] – age was considered at date of MRI; POCI: posterior circulation infarction; p value refers to results from bivariate analysis comparison between case and control groups, utilizing the independent t-test for continuous data and the pearson chi-square for categorical variables. Bold for p values translating statistical significance.

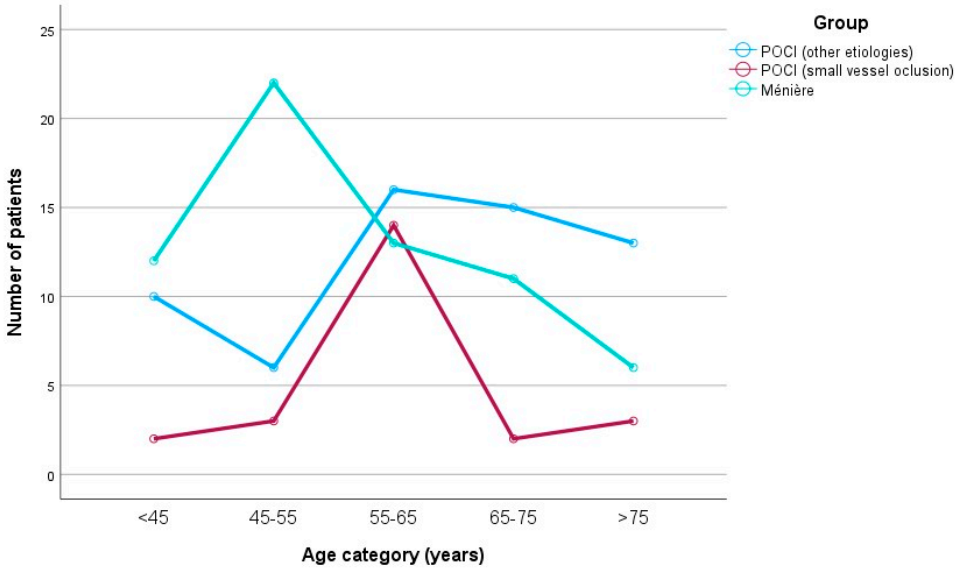


Figure 3. – Distribution of the sample by age category and type of pathology.

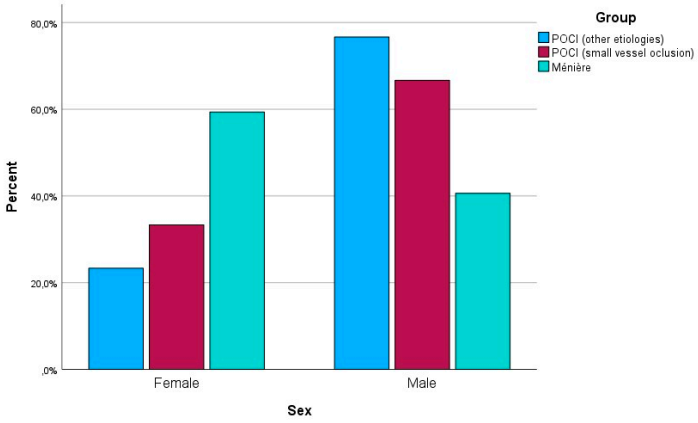
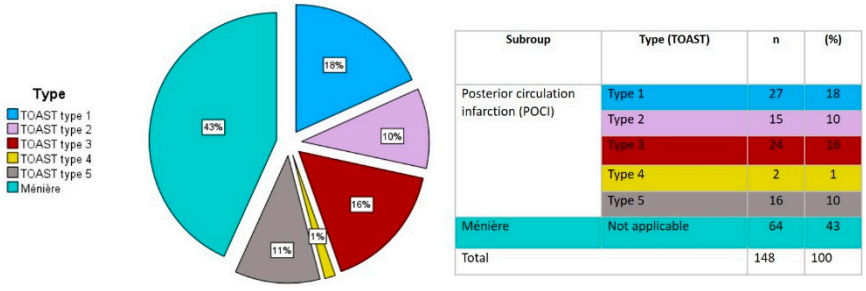


Figure 4. – Distribution of the sample by sex and type of pathology.



Subroup	Type (TOAST)	n	(%)
Posterior circulation infarction (POCI)	Type 1	27	18
	Type 2	15	10
	Type 3	24	16
	Type 4	2	1
	Type 5	16	10
Ménière	Not applicable	64	43
Total		148	100

Figure 5. - Distribution of the sample by subtype of pathology.

3.2. Ménière´s versus POCI: Risk Factors

The group comparison revealed a higher prevalence of various CVRF in POCI OE patients, namely Hypertension, Dyslipidemia, Diabetes Mellitus and smoking (see Table 2). The analysis was divided by age. Age < 45 years: MD vs patients with POCI SVO = p > 0.05 for all CVRF; MD vs patients with POCI OE: p = 0.029 for hypertension and p = 0. 011 for smoking (both higher in POCI OE); Age

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45-55: MD vs POCI SVO patients = p > 0.05 for all CVRFs; MD vs POCI OE patients: p = 0.043 for diabetes mellitus, p < 0.001 for hypertension, p = 0.048 for smoking (all higher in POCI OE); Age 55-65: MD vs POCI SVO patients = p > 0. 05 for all CVRFs, with the exception of dyslipidemia (higher prevalence POCI SVO, p = 0.003); MD vs patients with POCI OE: p = 0.047 for dyslipidemia; p =0.013 for smoking (both higher in POCI OE); Age 65-75: MD vs patients with POCI SVO = p >0.05 for all CVRFs; MD vs patients with POCI OE: p =0.024 for dyslipidemia (higher in POCI OE); Age > 75 years: MD vs patients with POCI SVO and MD vs patients with POCI OE = p > 0.05 for all CVRFs.

Table 2. Bivariate analysis of Ménière´s and posterior circulation infarction (POCI) groups concerning comorbidity prevalence within age categories.

Comorbidity	Age in years (category)	Prevalence			P value		
		Ménière (1)	POCI SVO (2)	POCI OE (3)	1 vs 2	2 vs 3	1 vs 3
Hypertension	< 45	25%	40 %	50 %	0.119	0.882	**0.029**
	45-55	13. 6 %	40 %	83.3 %	0.091	0.571	**< 0.001**
	55-65	46.2 %	71.4 %	68.75 %	0.182	0.873	0.219
	65-75	54.5 %	66.7%	86.7 %	0.224	0.582	0.068
	> 75	66.7 %	100 %	92.3 %	0.257	0.620	0.154
Diabetes Mellitus	< 45	8.3 %	5.2 %	10 %	0.672	0.593	0.350
	45-55	4.5 %	0 %	33.3 %	0.706	0.257	**0.043**
	55-65	50 %	37.5 %	23.1 %	0.148	0.491	0.404
	65-75	18.2 %	50 %	33.3 %	0.326	0.643	0.390
	> 75	33.3 %	0 %	23.1 %	0.257	0.356	0.637
Dyslipidemia	< 45	20 %	40 %	30 %	0.119	0.584	0.190
	45-55	31. 8 %	66.7 %	50 %	0.239	0.687	0.410
	55-65	38.5 %	92.9 %	75 %	**0.003**	0.190	**0.047**
	65-75	45.5 %	50 %	86.7 %	0.906	0.201	**0.024**
	> 75	50 %	66.7 %	53.8 %	0.635	0.687	0.876
Obesity	< 45	16.7 %	0 %	30 %	0.533	0.371	0.457
	45-55	9.1 %	33 %	16.7 %	0.225	0.571	0.595
	55-65	7.7 %	28.6 %	37.5 %	0.163	0.605	0.062
	65-75	18.2 %	50 %	6.7 %	0.326	0.074	0.364
	> 75	0 %	0 %	23.1 %	NC	0.356	0.200
Cardiac disease	< 45	8.3 %	0 %	0 %	0.350	0.462	0.350
	45-55	0 %	0 %	0 %	NC	NC	NC
	55-65	7.7 %	0 %	18.8 %	0.290	0.088	0.390
	65-75	0 %	0 %	20 %	NC	0.486	0.115
	> 75	33.3 %	33.3 %	38.5 %	1	0.869	0.829
Smoking	< 45	16.7 %	40 %	70 %	0.119	0.371	**0.011**
	45-55	0 %	16.7 %	66.7 %	0.529	0.134	**0.048**
	55-65	0 %	28.6 %	37.5 %	0.057	0.605	**0.013**
	65-75	0 %	0 %	20 %	NC	0.486	0.115
	> 75	16.7 %	33.3 %	15.4 %	0.571	0.473	0.943

NC: not computable; POCI: posterior circulation infarction; SVO: small vessel occlusion; OE: Other etiologies; Bold for p values translating statistical significance.

3.3. Cardiovascular Risk Factors and Stroke Risk: A Model

A multinomial logistic regression was performed to model the relationship between predictor variables (various CVRF and age) and membership in the three groups (Ménière, POCI SVO, POCI OE). With the addition of the predictor variables, the fit between the model including only the intercept and data improved, $\chi 2$ (14, N = 148) = 76.53, Nagelkerke R2 = 0.464, p < .001. As seen in Table 3, hypertension, dyslipidemia, and smoking each provided substantial distinct contributions. POCI OE was the reference group. As a result, each predictor contains two parameters: one for predicting

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Ménière group membership and one for predicting POCI SVO group membership. Table 4 displays the parameter estimates.

Table 3. Predictors unique contributions in the Multinominal Logistic Regression (N = 148).

Predictor	$\chi 2$	df	p-value
Hypertension	16.146	2	**< 0.001**
Diabetes Mellitus	1.140	2	0.566
Dyslipidemia	8.766	2	**0.012**
Obesity	0.589	2	0.745
Cardiac disease	4.625	2	0.099
Smoking	29.522	2	**< 0.001**
Age (years)	1.049	2	0.592

X^2 = amount by which -2 log likelihood increases when predictor is removed from the full model. Bold for p values translating statistical significance.

Table 4. Estimated parameter values when comparing the POCI OE group to the other groups (N = 148).

Predictor	POCI OE vs.	B	OR	p-value
Hypertension	Ménière´s disease	-2.070	0.126	**< 0.001**
	POCI SVO	-0.406	0.666	0.556
Diabetes Mellitus	Ménière´s disease	-0.173	0.841	0.750
	POCI SVO	0.507	1.660	0.371
Dyslipidemia	Ménière´s disease	-0.398	0.672	0.413
	POCI SVO	1.506	4.509	**0.024**
Obesity	Ménière´s disease	-0.455	0.635	0.446
	POCI SVO	-0.145	0.865	0.815
Cardiac disease	Ménière´s disease	-0.345	0.708	0.645
	POCI SVO	-2.008	0.134	0.074
Smoking	Ménière´s disease	-3.198	0.041	**<0.001**
	POCI SVO	0.285	1.330	0.630
Age	Ménière´s disease	-0.020	0.980	0.315
	POCI SVO	-0.003	0.997	0.913

POCI OE – posterior circulation infarction of other etiologies (not small vessel); POCI SVO: posterior circulation infarction due to small vessel occlusion; OR = odds ratio associated with the effect of a one standard deviation increase in the predictor. Bold for p values translating statistical significance.

When comparing the POCI OE group to the Ménière group, two of the predictors exhibited significant parameters: hyopertension and smoking. If the patient had hypertension, the odds of being in the POCI OE group rather than the Ménière group were 7 times greater (OR: 0.126, p <0.001, see Table 4). Likewise, if the patient was a smoker, the odds of being in the POCI OE group rather than the Ménière group were more than 20 times higher (OR: 0.041, p < 0.001, see Table 4). When comparing the POCI OE group to the POCI SVO group, only one predictor showed a significant parameter: dyslipidemia (see Table 4). In a patient with dyslipidemia, the odds of being in the POCI SVO group rather than the POCI OE group were four times higher (OR: 4.509, p = 0.024, see Table 4).

4. Discussion

Cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, smoking and obesity are well known causes of microvascular impairment, oxidative stress and compromise of the brain-blood and bloodlabyrinth barriers [22]. Although there are some important studies linking MD to CVRF [6,13], this association is still relatively unexplored. On the other hand, it remains unclear whether there are shared risk factors between Ménière's Disease (MD) and vertebrobasilar ischemic events. The need for better understanding the etiopathogenesis of MD along with the pertinency of unravelling new lines of investigation on MD motivated the present work.

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The primary research question was whether CVRF prevalence would differ between MD and POCI patients. The primary objective of the work was met. Higher prevalence of Hypertension, Diabetes Mellitus, Dyslipidemia and smoking was found in POCI OE patients compared to MD in various age categories.

Conversely, no significant differences were found regarding the prevalence of CVRF between MD and POCI SVO, with the exception of Dyslipidemia within the 45-55 age category. The multivariate model further reinforced such findings, while supporting the role of dyslipidemia in POCI SVO. These results suggest a partial overlap in CVRF prevalence between MD and POCI SVO, as opposed to non-small vessel disease (POCI OE), where CVRF prevalence was more pronounced. Importantly, the similarity in CVRF´s prevalence between MD and POCI SVO frame the possibility of microvascular dysregulation as a common contributor in these two entities.

Well-known target end-organs of cardiovascular disease such as the brain, heart, kidney or the eye have already been described [22–24]. Nevertheless, a lot less is known concerning microvascular affection of the inner ear. Since microvascular dysfunction is pointed as a systemic disorder [23] it seems licit to consider that the inner ear may not be an exception [22]. There are two main potential pathways in which microvascular disease could relate to MD. One would be by increasing the risk of EH (etiopathogenic theory); the other by enhancing attacks in an already hydropic ear (attack-triggering theory) [25].

There are some arguments in favor of the etiopathogenic pathway. Microvascular dysfunction has been associated with various markers common to both typical end-target organs (brain, heart, kidney) and the inner-ear. Aquaporins, adducins, dermatopontin and potassium voltage-gated channel subunits are some examples [1,11,23,26]. Many endolymph-bound ion transport channels have been shown to be controlled by hormonal processes such as β-adrenergic, muscarinic, and purinergic receptors. [27,28]. However, the relationship between ion transport and endolymph ion concentration and volume remains unknown. Only an osmotic inflow of water may cause a volume change. Aquaporins, which are expressed in the inner ear, have a function in water equilibration across endolymphatic borders and are regulated by hormones [3]. In fact, vasopressin (V2) receptors have been found in the inner ear and may balance water flow by control of aquaporin expression, in a mechanism similar to the Kidney [3]. Nevertheless, it is still unclear how this system is regulated and what are the exact roles of the various inner ear structures [3]. MD etiology has already been linked to a variety of genes involved in ionic composition, water transport, and cardiovascular development [1,11,26].

Endothelial dysfunction, inflammation (including reactive oxidation), immunological activation, and coagulation are all possible mechanisms driving systemic microvascular dysfunction [23]. In fact, a recent study of the human utricle´s macula microvasculature demonstrated that vascular endothelial cells and pericytes are damaged in MD [18,29]. Two oxidative stress markers have been implied in such damage: inducible nitric oxide synthase (iNOS) and nitrotyrosine. These markers have been found in vascular endothelial cells of BLB from MD patients suggesting that oxidative stress is involved in BLB disruption [30]. Recent research in BLB pathophysiology emphasizes the relevance of BLB integrity for ion and water homeostasis [31–33], suggesting that BLB dysfunction is important in understanding the pathophysiology of EH and possibly MD.

The attack-triggering theory, on the other hand, proposes that hydrops operates as a variable starling resistor on the inner ear vasculature, capable of generating ischemic episodes in those with low ear perfusion pressure [6]. An animal experiment showed that MD attacks are not caused by EH itself, but they can be provoked by decreased vascular flow in the inner ear [34]. The BLB is essential for maintaining inner ear fluid ionic equilibrium [18]. In case of hydropic ear transient ischemia, resulting BLB disruption could activate deleterious mechanisms culminating in the MD attack. Moreover, ischemia and hypoxia cause fast calcium translocation from extracellular to intracellular regions in brain tissues [3]. Since endolymph calcium has been shown to influence transduction in hair cells, it is possible that calcium influx in the setting of inner ear hypoxia contributes to the functional losses observed in MD attacks [3].

This study has its strengths. It is the first to compare a MD with a POCI population from a cardiovascular point of view. It includes a relatively large sample of patients (both MD and POCI) formerly submitted to brain imaging. Also, it underscores microvascular dysregulation as a potential novel mechanism for MD development and/or progression.

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It is essential to acknowledge some limitations of our study. Firstly, the retrospective nature of this research may incur in selection bias. Secondly, it would be pertinent to include an age-matched "control" group without MD or POCI to further validate our results and check for asymmetries in the prevalence of CVRF between MD and the general population. Considering broader demographic variations in future studies could offer more comprehensive insights into the applicability of the findings across different populations. Also, since clinical data was derived from pre-existing records, it is possible that certain comorbidities were overlooked. Additionally, since the POCI SVO group included a relatively small number of patients, comparison with the MD population may have been statistically affected. It is important to note that the duration of risk factors such as hypertension, diabetes mellitus, smoking, and related indices, including smoking index, could not be precisely ascertained due to limitations in the available database. The absence of this information represents a constraint in our analysis and necessitates cautious interpretation of the results with regard to the temporal aspects of risk factor exposure. Therefore, the authors consider that results should be regarded thoughtfully and validated by further larger, prospective studies.

5. Conclusions

In conclusion, this study compared cardiovascular risk factors in Ménière's disease (MD) and posterior circulation infarction (POCI) patients. Similar cardiovascular risk factors' (CVRFs) prevalence was observed between MD and small vessel POCI (POCI-SVO), with the exception of dyslipidemia in the 55-65 age group. More notable disparities were evident in larger vessel POCI cases (POCI-OE), with odds of POCI OE more significantly associated with hypertension and smoking in the multivariate analysis. This work points to the potential for exploring determinants of microvascular dysregulation in Ménière's Disease. While the exact MD´s pathophysiologic mechanisms remain unknown, it is possible that MD patients share common ground with thrombotic microangiopathy entities such as POCI-SVO. Finally, further research is needed on this topic. New future findings could have substantial clinical influence, given that an early preventive action on CVRF´s or its adequate treatment would potentially improve MD´s care and prognosis. Considering the complex interplay of factors involved, exploring collaborations across disciplines like otolaryngology, neurology, and primary care could offer valuable insights.

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