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Cardiovascular risk factors among patients with acute unilateral inner ear hypofunction: A case–control study

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Abstract

Objectives: To assess the prevalence of cardiovascular risk factors (CVRFs) and their impact on acute unilateral inner ear hypofunction (AUIEH), including acute unilateral peripheral vestibulopathy (AUPVP), sudden sensorineural hearing loss (SSNHL) and acute unilateral audiovestibular hypofunction (AUAVH).

Methods: One hundred and twenty-five patients consecutively diagnosed with AUPVP, SSNHL or AUAVH and 250 sex- and age-matched controls were included. Cases presented a mean age of 58.6 ± 14.7 years and included 59 women and 66 men. The correlation between CVRFs (high blood pressure [HBP], diabetes mellitus [DM], dyslipidemia [DLP], cardiocerebrovascular disease [CCVD]) and AUIEH was assessed by multivariate conditional logistic regression analysis.

Results: A higher prevalence of CVRFs was identified in patients than in controls (30 individuals with DM, 53 with HBP, 45 with DLP and 14 with a previous history of CCVD, $p < .05$). A significantly elevated risk of AUIEH was found in patients with two or more CVRFs (adjusted odds ratio [OR] 5.11; 95% CI 2.23–11.70). Previous CCVD individually predicted AUIEH (OR 8.41; 95% CI 2.36–29.88). Subgroup analysis showed the same tendency for AUPVP and SSNHL.

Conclusion: Acute unilateral inner ear hypofunction patients presented significantly more CVRFs than controls, and the presence of two or more CVRFs was associated with AUIEH. Future studies evaluating vascular risk in AUIEH may include AUPVP and SSNHL patients from the same source population to better characterize risk profiles that can indicate a vascular origin.

Level of Evidence: 3b

KEYWORDS

acute unilateral peripheral vestibulopathy, cardiocerebrovascular disease, cardiovascular risk factors, sudden sensorineural hearing loss

1 | INTRODUCTION

Acute unilateral inner ear hypofunction (AUIEH) can develop as a result of a global impairment of function (labyrinthitis/acute unilateral audiovestibular hypofunction [AUAVH]) or a partial disorder, leading to acute unilateral peripheral vestibulopathy (AUPVP) or sudden sensorineural hearing loss (SSNHL).

Acute unilateral vestibular hypofunction, presenting as vestibular neuritis, is one of most frequent causes of vertigo of peripheral origin.[1,2] A previous upper airway infection or concomitant findings of viral infection point toward a viral etiology. Reactivation of herpes simplex virus in the vestibular ganglia is considered an important trigger.[3] However, there is often no detectable etiology, and other hypotheses have been proposed, including thrombosis and an autoimmune inner ear reaction.[2,3] Clinically, unsteadiness is verified with a spontaneous horizontal nystagmus beating away from the lesion side, with a positive head impulse test and a caloric paresis on the affected side.[4]

Sudden sensorineural hearing loss (SSNHL) is an acute condition characterized by a decrease in hearing of ≥30 decibels affecting at least three consecutive frequencies within 72 h or less, requiring urgent treatment.[5] Proposed triggers include infectious, autoimmune, vascular and metabolic diseases, but an origin is identified in only 10%–30% of the cases, and there is no sufficient evidence of a higher likelihood of any origin over another.[5,6] The estimated incidence is at least 5–20 per 100,000/year, and the spontaneous recovery rate is 32%–65%.[7] Interestingly, epidemiological studies show that the incidence of SSNHL is increasing.[6] Similar to AUPVP, previous upper airway infection or concomitant findings of viral infection point toward a viral etiology. However, as in AUPVP, the majority of patients do not have this profile. This might explain why steroids and antiviral treatments do not dramatically change disease outcomes.[8] Thus, in the absence of an identifiable cause, the pathology of SSNHL, AUPVP, and AUAVH has yet to be elucidated.

As previously described, dysfunctions in the blood supply of the inner ear can impair fluid homeostasis and may be related to SSNHL, autoimmunity, age-related hearing loss and AUPVP.[9]

The inner ear is supplied by the labyrinthine artery, which is an end artery that overlaps with inner ear innervation. A sudden interruption of blood flow of the anterior vestibular artery will affect the same structures of a superior vestibular nerve inflammation, and the symptoms could be the same in an inflammatory or vascular insult.[2] Moreover, the labyrinth is vulnerable to ischemia due to its high-energy metabolism, and smoking and poorly controlled diabetes mellitus were shown to be associated with hearing impairment.[10]

Consequently, it is reasonable to theorize that acute thrombotic events can occur in inner ear atherosclerotic vessels.[11] It was proposed that patients with SSNHL have a higher risk of developing cardiocerebrovascular disease, while stroke patients have a 71% increased risk of developing SSNHL.[8,12] However, other works affirm that SSNHL is not a predictor of initial acute myocardial infarction (AMI).[13] Recently, some systematic reviews assessed the prevalence of cardiovascular risk factors (CVRFs) and cardiovascular events among AUPVP and SSNHL patients.[2,14,15] Their results showed a higher prevalence of vascular risk factors among AUPVP patients and an association between SSNHL and a higher vascular risk profile. High levels of triglycerides and total cholesterol were linked to a higher risk of developing future stroke in SSNHL patients. However, high levels of data heterogeneity were observed.

Cardiovascular risk factors are divided into two major classes: nonmodifiable (age, sex, and family history) and modifiable risk factors (high blood pressure [HBP], use of tobacco, diabetes mellitus [DM], physical inactivity, unhealthy diet, and dyslipidemia [DLP]).[11]

Various studies assessed CVRFs in patients with AUPVP and SSNHL but as individual and separated inner ear events. In this work, we studied the CVRFs in AUIEH patients considering that AUPVP and SSNHL might have common pathophysiological mechanisms, at least in some high-vascular-risk patients, taking into account previous results.[2,14,16] The aim of this retrospective case–control study was to assess CVRFs and vascular events in a population with AUIEH, including acute isolated vestibular or auditory loss and global inner ear hypofunction. The primary outcome was the prevalence of three modifiable CVRFs (DM, HBP, and DLP) in AUIEH patients compared to that in controls and the influence of the number of CVRFs on AUIEH occurrence. The secondary outcome was differences in a previous history of cardiocerebrovascular disease (CCVD, coronary artery disease and/or stroke) between patients and controls.

2 | MATERIALS AND METHODS

We conducted a retrospective chart review of all patients diagnosed with AUPVP, SSNHL or AUAVH in our institution between 2017 and 2021. A control group was recruited from the surgical database and electronic medical records of our institution during the same period. The electronic health care records were reviewed to collect the following data: demographics, diagnosis and cardiovascular comorbidities.

2.1 | Ethics statement

The Institutional Review Board waived the requirement of approval for this retrospective chart review study (OM 174), and the research was performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments. The patient records and information were anonymized before analysis. This report followed the STrenghening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

2.2 | Patient group

We retrospectively reviewed the records of 125 patients consecutively diagnosed with AUPVP, SSNHL or AUAVH in our institution between January 2017 and December 2021. Patients were evaluated

with an otolaryngological examination, initial and follow-up pure tone audiometry (PTA), magnetic resonance imaging (MRI) when indicated, and initial and follow-up vestibular testing if vestibular symptoms were present (video nystagmography, video head-impulse test). The exclusion criteria included the following: previous surgery in the affected ear, fluctuation in hearing loss, bilateral SSNHL, a prior history of hearing loss or chronic otitis media, acoustic trauma history, posterior cranial fossa tumors or history of nasopharyngeal carcinoma. The following data were extracted: the patient's sex, age at initial treatment, presenting symptoms, the time from the onset of symptoms to presentation for treatment, initial hearing level/vestibular testing at presentation in the hospital and past medical history, including DM, DLP, HBP and previous history of stroke and/or coronary artery disease (CCVD). Hypertension was defined when patients were taking antihypertensive medications for HBP, if their systolic blood pressure was 140 mmHg or more, or if their resting diastolic blood pressure was 90 mmHg or more on several measurements spread over time in medical records.[17] Diabetes was considered if patients were taking medical treatments for diabetes, if they had a fasting serum glucose level of 126 mg/dl or more, if they had a nonfasting random serum glucose level of 200 mg/dl or more, or if they had a whole blood glycated hemoglobin level of 6.5% or more on several measurements spread over time. Subjects were diagnosed with DLP if they had a fasting total cholesterol level of 240 mg/dl or more or if they were being treated with a lipid-lowering agent.

Sudden sensorineural hearing loss was defined as a sensorineural hearing loss of at least 30 dB in three consecutive speech frequencies that occurred within the previous 3 days.[5] Acute unilateral vestibular hypofunction patients were diagnosed when the full following criteria were present: (1) acute vertigo lasting for at least 24 h, (2) absence of auditory complaints, (3) horizontal unidirectional nystagmus present during physical examination, (4) absence of neurological symptoms or signs, and (5) evidence of vestibular deficit observed by head impulse test.

Acute unilateral audiovestibular hypofunction was diagnosed when patients had evidence of both vestibular hypofunction and acute sensorineural hearing loss, without other identifiable origin. All patients were observed in ENT consultations in the first 7 days after symptom onset.

All SSNHL patients were treated with oral prednisolone or equivalent, and some patients were submitted to salvage therapy with either an intratympanic steroid (dexamethasone) injection weekly for 3 weeks or hyperbaric oxygen therapy, according to previously published guidelines.[5] AUPVP patients were submitted to symptomatic treatment with or without steroids and vestibular rehabilitation as soon as possible. However, assessing the outcomes of these interventions was not the aim of this study. All patients were followed up for at least 3 months.

2.3 | Control group

The comparison group included consecutive adult (>18 years old) patients admitted for ENT surgical procedures (septoplasty, turbinoplasty, functional endoscopic sinus surgery for symptomatic nasal obstruction and/or chronic rhinosinusitis, and tonsillectomy) during the same period. Previously, hospital-based patients undergoing elective outpatient surgery were proposed as an adequate population for control group recruitment, namely, as a control group for an SSNHL cohort.[18–20] All patients were assessed in a preoperative anesthetic visit with a systematic medical history questionnaire. The following data were extracted: the patient's sex, age at initial presentation at this appointment and past medical history, including DM, DLP, HBP, and previous history of vascular events such as stroke and coronary artery disease. The definitions of the risk factors in controls were the same as those for patients. The control participants were matched in a 1 patient:2 control ratio by age and sex. The same exclusion criteria applied to both groups.

2.4 | Statistical analysis

The data were analyzed by Stata IC16 software (StataCorp LP, College Station, TX, USA). Continuous variables are expressed as the mean

TABLE 1 Demographic characteristics of subjects included in the study

	Cases ($n = 125$)	Controls ($n = 250$)	p value
Age, years (mean ± *SD*, range)	58.6 ± 14.7 (20–88)	57.8 ± 14.1 (21–89)	.293*
Women (*n* [%])	59 (47.2)	118 (47.2)	1.0**
Men (*n* [%])	66 (52.8)	132 (52.8)	
High blood pressure (*n* [%])	53 (42.4)	48 (19.2)	<.001**
Diabetes mellitus (*n* [%])	30 (24)	12 (4.8)	<.001**
Dyslipidemia (*n* [%])	45 (36)	30 (12)	<.001**
Cardiocerebrovascular disease (*n* [%])	14 (11.2)	4 (1.6)	<.001**
- Stroke	0 (0)	3 (1.2)	.219**
- Coronary artery disease	14 (11.2)	1 (0.4)	<.001**

Abbreviation: *SD*, standard deviation.
*Student *t* test;
**Chi-square test.

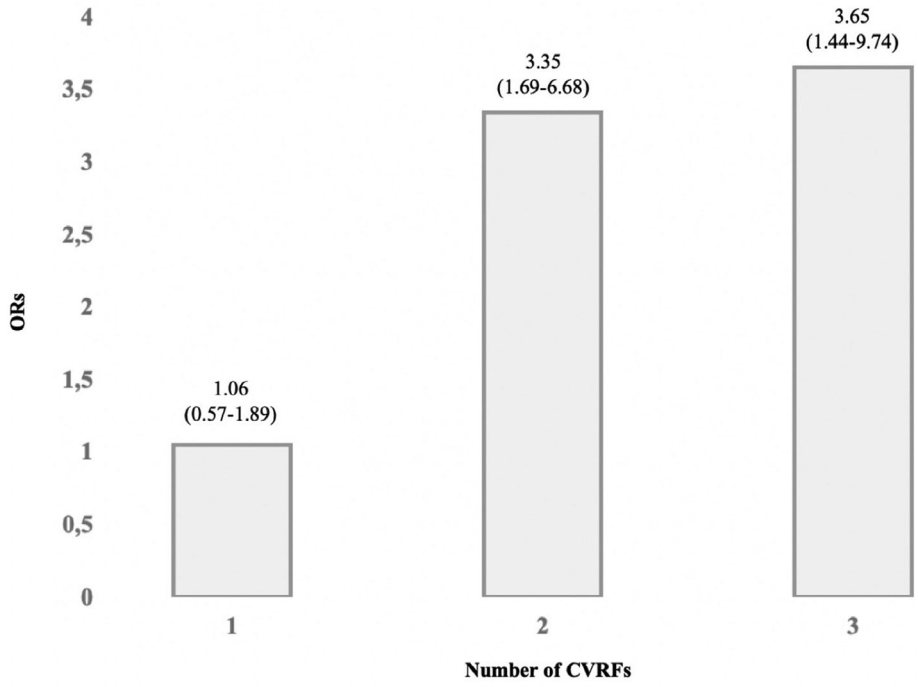


FIGURE 1 Probability (unadjusted odds ratio, 95% confidence interval [95% CI]) of acute unilateral inner ear hypofunction according to the number of cardiovascular risk factors

TABLE 2 Multivariable conditional logistic regression analysis for AUIEH according to evaluated CVRFs

	Adjusted OR	95% CI	*p* value
High blood pressure	1.05	0.45–2.45	.906
Diabetes mellitus	1.31	0.47–3.64	.597
Dyslipidemia	1.42	0.79–2.58	.239
Cardiocerebrovascular disease	8.41	2.36–29.88	.001

Abbreviations: AUIEH, acute unilateral inner ear hypofunction; CI, confidence interval; CVRF, cardiovascular risk factor; OR, odds ratio.

TABLE 3 Multivariable conditional logistic regression analysis for AUIEH according to the number of CVRFs

Number of CVRFs (*n* for cases)	Adjusted OR	95% CI	*p* value
One CVRF (23)	1.86	0.96–3.59	.062
Two CVRFs (27)	5.11	2.23–11.70	<.001
Three CVRFs (15)	5.80	1.95–17.21	.002

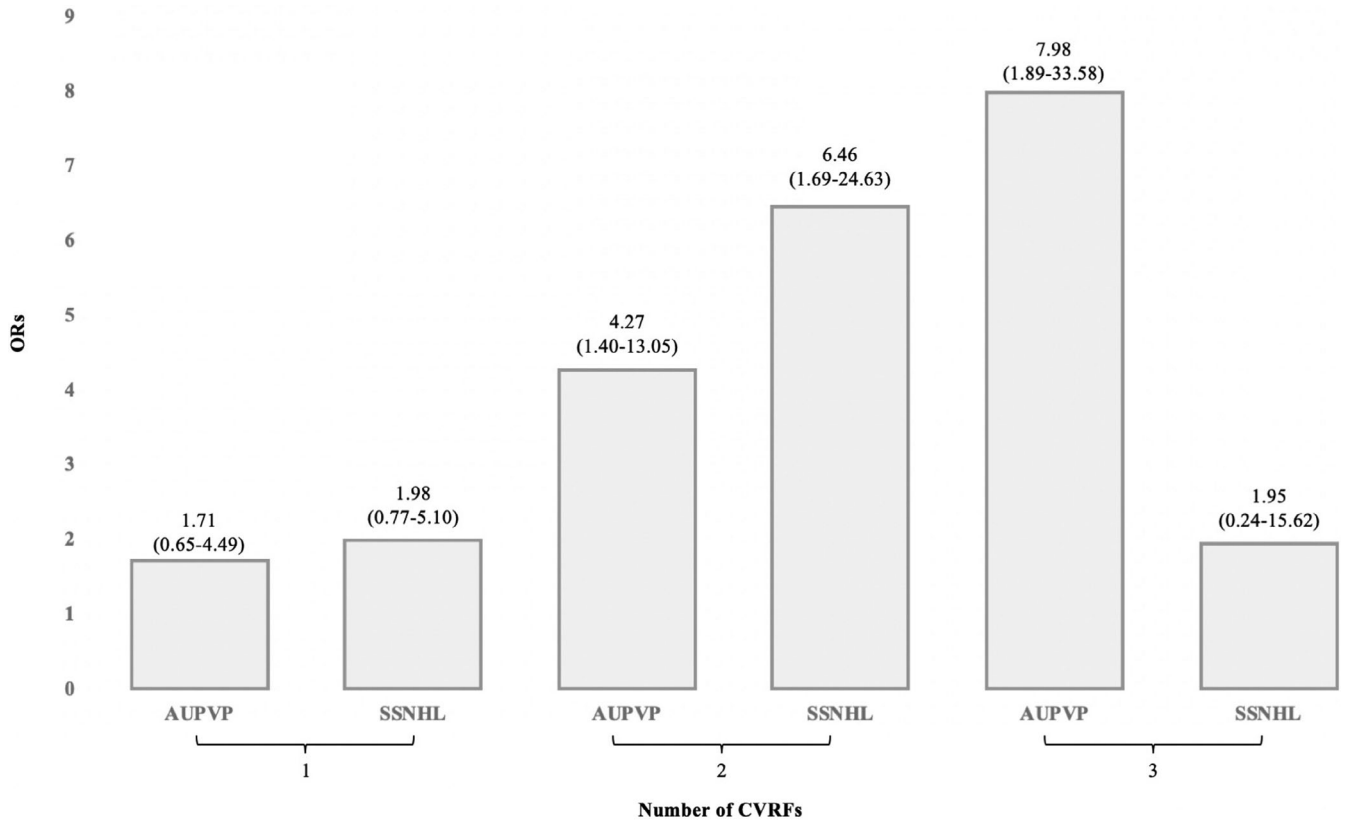
Abbreviations: AUIEH, acute unilateral inner ear hypofunction; CI, confidence interval; CVRF, cardiovascular risk factor; OR, odds ratio.

± standard deviation and range, while categorical variables are expressed as frequencies. Contingency table analysis comparing rates between matched samples was performed using the chi-squared test or Fisher's exact test, as indicated. Student's *t* test was used to compare means between groups. To assess the association between AUIEH and the hypothesized risk factors (CVRFs and CCVD), odds ratios and 95% confidence intervals were calculated through conditional logistic regression to take into account the matched design. Sample size estimation was performed considering a DLP prevalence of 6% in controls and a DM prevalence of 7% in controls.[21,22] With an alpha of 0.05 and a power of 80%, a sample of 66 patients and 66 controls would provide power to detect a significant difference between groups, and a group of 121 patients and 242 controls would provide power to detect an OR equal to or greater than 2.64 for the likelihood of DM. For all the tests used, a value of $p < .05$ was considered significant.

TABLE 4 Prevalence of CVRFs in subgroups of AUPVP and SSNHL

Subgroup	Cases	Controls	*p* value
AUPVP	69	250	
High blood pressure (*n* [%])	29 (42)	48 (19.2)	<.001*
Diabetes mellitus (*n* [%])	15 (21.7)	12 (4.8)	<.001*
Dyslipidemia (*n* [%])	24 (34.8)	30 (12)	<.001*
Cardiocerebrovascular disease (*n* [%])	9 (4.6)	4 (1.6)	<.05*
SSNHL	49	250	
High blood pressure (*n* [%])	21 (42.8)	48 (19.2)	<.001*
Diabetes mellitus (*n* [%])	13 (26.5)	12 (4.8)	<.001*
Dyslipidemia (*n* [%])	19 (38.8)	30 (12)	<.001*
Cardiocerebrovascular disease (*n* [%])	5 (10.2)	4 (1.6)	<.05*
AUAVH	7	250	
High blood pressure (*n* [%])	3 (42.8)	48 (19.2)	.143**
Diabetes mellitus (*n* [%])	2 (28.5)	12 (4.8)	.050**
Dyslipidemia (*n* [%])	2 (28.5)	30 (12)	.212**
Cardiocerebrovascular disease (*n* [%])	0 (0)	4 (1.6)	.895**

Abbreviations: AUAVH, acute unilateral audiovestibular hypofunction; AUPVP, acute unilateral peripheral vestibulopathy; SSNHL, sudden sensorineural hearing loss.
*Chi-square test; **Fisher's exact test.



AUPVP acute unilateral peripheral vestibulopathy; *CVRFs* Cardiovascular risk factors; *ORs* odds ratios; *SSNHL* sudden sensorineural hearing loss

FIGURE 2 Probability (multivariable conditional logistic regression, adjusted odds ratios, 95% confidence interval [95% CI]) of acute unilateral peripheral vestibulopathy and sudden sensorineural hearing loss according to the number of cardiovascular risk factors

3 | RESULTS

Among the 125 included patients, a total of 69 patients had a diagnosis of AUPVP, 49 patients had SSNHL, and 7 patients had AUAVH. The main characteristics of the included individuals are presented in Table 1. In the patient group, 53 patients (42.4%) presented HBP, 30 (24%) presented DM, 45 (36%) had DLP and 14 (11.2%) had a previous history of CCVD.

3.1 | Diabetes mellitus, high blood pressure, dyslipidemia and previous history of CCVD

The frequencies of HBP, DM and DLP were all higher in the case group than in the control group ($p < .001$, Table 1). For CCVD, a higher prevalence was also found in the patient group due to the high prevalence of coronary artery disease cases ($p < .001$). Stroke cases were more prevalent in controls but without a significant difference.

When assessing the probability of AUIEH according to the number of CVRFs, a trend of higher odds was verified with an increasing number of CVRFs (unadjusted ORs between 1.06 and 3.65, chi-square, $p < .05$ for two or more CVRFs, Figure 1).

In multivariable analysis, when assessing CCVD and each CVRF individually, only the former was independently associated with AUIEH (Table 2). On the other hand, when evaluating the influence of the number of CVRFs on AUIEH occurrence, the presence of 2 or more CVRFs was significantly associated with a higher odds of AUIEH (Table 3).

3.2 | Subgroup analysis

In the subgroup analysis of cases compared with the age- and sex-matched controls, the prevalence of CVRFs and CCVD was significantly higher in AUPVP and SSNHL patients (Table 4).

Regarding the influence of the number of CVRFs on AUPVP and SSNHL occurrence, a significant tendency toward higher disease risk was verified for patients with an increasing number of CVRFs (two or more in AUPVP and two in SSNHL, adjusted ORs between 1.71 and 7.98, chi-square, $p < .05$, Figure 2). For AUAVH, no statistically significant differences were found in this small sample of patients, but a tendency toward a higher prevalence of CVRFs was observed in cases.

Through multivariable conditional logistic regression considering all factors, a higher risk of AUIEH was associated with a previous history of CCVD but was only significant for AUPVP, with an adjusted OR of 5.68 (95% CI 1.01–31.7), whereas it was 3.44 (95% CI 0.29–40.71) for SSNHL.

To assess if older patients skewed results (probably with a more pronounced prevalence of cardiovascular disease), the CVRFs and CCVD analysis were stratified by age subgroups (less than 40 years old and 40 years of age or older). Only HBP and DLP presented a more significant prevalence in individuals 40 years of age or older ($p < .05$). The presence of CCVD, DM, and the number of CVRFs did not significantly differ between these two age groups. Additionally, the inclusion of this age subgroup in multivariable conditional logistic regression did not influence the results. A higher risk of AUIEH persisted linked to a previous history of CCVD (adjusted OR of 7.07 [95% CI 2.25–22.25]).

4 | DISCUSSION

This study investigated the prevalence of DM, HBP, and DLP in AUIEH patients compared to matched controls and the influence of the number of CVRFs on AUIEH occurrence. Previous CCVD was also analyzed in cases and controls. A subgroup analysis was performed to evaluate whether differences were present between the three groups of inner ear acute disease. Overall, all assessed CVRFs were more prevalent in the AUIEH group than in the control group, and a tendency toward a higher risk of AUIEH was found in patients with two or more CVRFs (adjusted OR 5.11; 95% CI 2.23–11.70 and OR 5.80; 95% CI 1.95–17.21, respectively). All variables were considered in multivariable conditional logistic regression, and only previous CCVD individually predicted AUIEH (OR 8.41; 95% CI 2.36–29.88). Subgroup analysis showed that the results were equivalent in AUPVP and SSNHL, with a statistically significant tendency toward having a higher disease risk if patients presented two CVRFs (multivariable conditional logistic regression adjusted OR 4.27; 95% CI 1.40–13.05 and OR 6.46; 95% CI 1.69–24.63, respectively). Older patients did not influence the results of the multivariable conditional logistic regression maintaining the higher risk of AUIEH when a previous history of CCVD was reported.

Previously, other works verified a higher prevalence of CVRFs in AUPVP and SSNHL patients. Based on a cross-sectional retrospective study of 160 AUPVP patients, Oron et al. concluded that HBP, DM, DLP, ischemic heart disease and prior stroke were significantly associated with AUPVP, but no matched controls were used. Instead, the ratio of CVRFs among patients was compared to the ratio of those among the general Israeli population published in the literature.[21] Han et al. did not find significant differences in HBP, DM, or DLP between AUPVP patients and controls. Nevertheless, the prevalence of carotid plaques was significantly higher in AUPVP patients.[23] However, this study has an important limitation: the ratio of controls to patients was below 1:1 (74 controls for 90 patients).

Regarding SSNHL, previous studies from large-scale population administrative databases provided evidence for a higher prevalence of CVRFs in SSNHL patients.[24,25] A meta-analysis including these studies proposed hypertriglyceridemia and hypercholesterolemia as potential independent risk factors for SSNHL.[14] However, susceptibility to methodological inconsistencies was mentioned as a potential limitation of these results. Smaller case–control studies also concluded a higher prevalence of DM in SSNHL patients.[13,25] Mixed results were verified for HBP and DLP,[13,22,25] but the number of metabolic syndrome components was found to increase the risk of SSNHL in 81 patients.[22] A risk of future stroke was identified in SSNHL patients,

and a previous history of CCVD was verified to be more prevalent in AUPVP patients.[15,21] However, no predictive analysis was made before for CCVD. In the present study, we added evidence of a previous history of CCVD showing that it was independently associated with AUPVP (multivariable conditional logistic regression adjusted only significant for AUPVP with adjusted ORs of 5.68; 95% CI 1.01–31.7, and 3.44; 95% CI 0.29–40.71 for SSNHL). In our cases, only coronary disease contributed to these results (Table 1).

To address some potential sources of bias, we included controls undergoing different surgical procedures not related to the exposure and who were recommended for surgery but not necessarily submitted to surgery depending on the anesthetic risk assessed at the preoperative visit. This reduces the potential bias of performing surgery in healthier patients. In fact, the control group included patients with a previous history of stroke, which was not observed in our AUIEH patients, showing that this potential bias might be limited. To minimize selection bias, diseases indicated for surgery in the control group had similar referral patterns as those identified for the cases. Chronic rhinosinusitis was linked to an increased risk of stroke and acute myocardial infarction mediated by the inflammatory context.[26,27] This evidence could influence our secondary outcome but not the primary outcome. Indeed, four cases of stroke were found in the control group, and the results between cases and controls may be underestimated. They might be more significant if population-based controls were used.

Regarding the representativeness of our controls for the prevalence of HBP, DLP and FM in the Belgian population, we detected a real prevalence of 20% for HBP,[28] 14% for DLP[29] and 6.6% for DM.[30] Thus, our control group shows approximated prevalences for HBP (19.2%), DLP (12%) and DM (4.8%).

As explained above, an effort was made to address potential sources of bias, namely, from the control group. However, this study presents other limitations, namely, due to its retrospective nature. In addition, only three CVRFs were analyzed, when factors such as tobacco smoking, obesity, physical inactivity and types of DLP could also influence the results. The small sample size of the AUAVH also did not allow for solid conclusions to be reached. Audiograms were not performed in controls. Thus, there is the possibility for some patients to have prior hearing loss that was the result of a prior sudden hearing loss event, without a significant subjective loss and then not reported by the patient during clinical assessment. Moreover, the CVRF prevalence in the control group may be slightly inferior to the real prevalence.

This work is based on clinical data from consecutive patients and focuses on CVRFs in patients with AUIEH considering AUPVP and SSNHL together from the same source population. Additionally, the influence of the number of CVRFs on AUPVP was not previously reported.

5 | CONCLUSION

This study showed that AUPVP and SSNHL might share similar trends regarding vascular risk. However, caution in interpreting the results is needed considering the limitations of our study. Future studies evaluating the influence of CVRFs in acute inner ear dysfunction may include AUPVP and SSNHL patients to better characterize high-risk profiles that can indicate a vascular origin and eventually a higher risk of future vascular events.

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AUTHOR CONTRIBUTIONS

Conceptualization: João Simões, António Miguéis, Frederic Acke. **Data curation:** João Simões, António Miguéis, Frederic Acke, Raquel Seiça. **Formal analysis:** João Simões, António Miguéis, Frederic Acke. **Investigation:** João Simões, António Miguéis, Stephan Vlaminck. **Methodology:** João Simões, António Miguéis, Frederic Acke. **Project administration:** João Simões. **Software:** João Simões. **Supervision:** António Miguéis, Stephan Vlaminck, Raquel Seiça. **Writing – original draft:** João Simões, António Miguéis. **Writing – review & editing:** Frederic Acke. Stephan Vlaminck, Raquel Seiça.

CONFLICT OF INTEREST

There are no financial conflicts of interest to disclose.

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