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STUDY OF THE CLINICAL ASSOCIATION BETWEEN AUDIOVESTIBULAR HYPOFUNCTION AND VASCULAR EVENTS

Tese no âmbito do Programa Doutoral em Ciências da Saúde, ramo de Medicina, orientada pelo Professor Doutor António Carlos Eva Miguéis e pela Professora Doutora Raquel Maria Fino Seiça e apresentada à Faculdade de Medicina da Universidade de Coimbra.

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Study of the clinical association between audiovestibular hypofunction and vascular events

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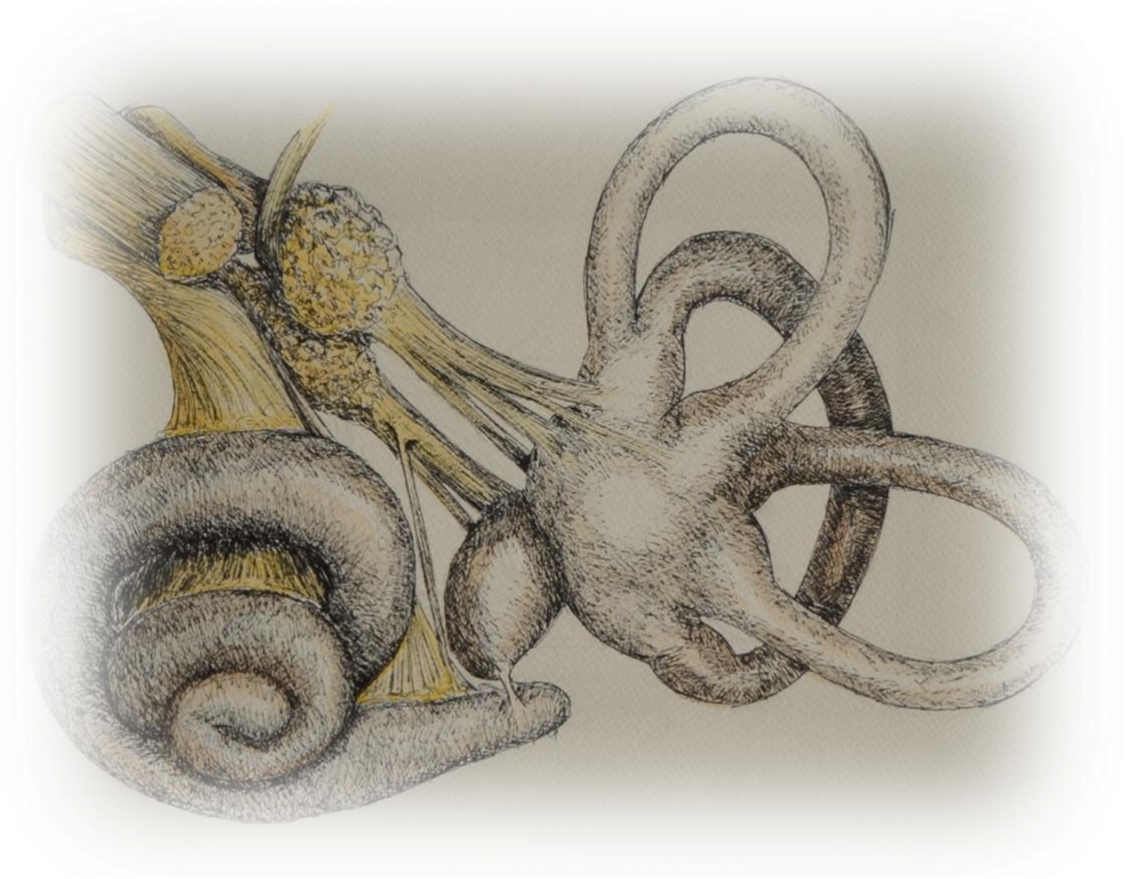

Mathilde Vercruysse, 2022

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List of abbreviations used in this thesis

AICA anterior inferior cerebellar artery
ARHL age-related hearing loss
AUAVH acute unilateral audiovestibular hypofunction
AUIEH acute unilateral inner ear hypofunction
AUPVP acute unilateral peripheral vestibulopathy
AVA anterior vestibular artery
BPPV benign paroxysmal positional vertigo
CAD coronary artery disease
CCA common cochlear artery
CCVD cardiocerebrovascular disease
CVA cerebrovascular accident
CVRFs cardiovascular risk factors
dB HL decibels hearing loss
DLP dyslipidemia
DM diabetes mellitus
HBP high blood pressure
HDL-c high-density lipoprotein cholesterol
IHC inner hair cells
IHD ischemic heart disease
LA labyrinthine artery
LDL-c low-density lipoprotein cholesterol
LFHL low-frequency hearing loss
MetS metabolic syndrome
MI myocardial infarction
MRI magnetic resonance imaging
OHC outer hair cells
OR odds ratio
PTA pure tone audiometry
SSNHL sudden sensorineural hearing loss
TG triglycerides
TIA transient ischemic attack
VEMPs vestibular-evoked myogenic potentials
vHIT video head impulse test
VN vestibular neurit

Publication List

1 Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review

Simões J, Vlaminck S, Seiça R, Acke F, Miguéis, A.. Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review. Acta Otorhinolaryngol Ital 2021; 41: 401-409. doi: 10.14639/0392-100X-N1543

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2 Cardiovascular risk and sudden sensorineural hearing loss: a systematic review and meta-analysis

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3 Cardiovascular risk factors among patients with acute unilateral inner ear hypofunction: a case-control study

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4 Audiometric patterns and vascular risk in age-related hearing loss

João Simões, Stephan Vlaminck, Raquel Seiça, Frederic Acke, António Miguéis

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Abstract

The differential diagnosis of acute audiovestibular diseases is vast, including viral infections tumors, autoimmunity, and others. The link between these acute inner ear events and cardiovascular risk factors (CVRFs) has been analyzed. Studies hypothesized that inner ear acute events might be a clinical outcome of thrombotic and hemorrhagic disease of the end-artery type of the inner ear. The increasing performance of medical imaging has allowed diagnostic inner ear acute vascular inner ear events like bleeding and cochleovestibular infarction. Studying the potential links between acute inner ear hypofunction and CVRFs may allow the detection of high-risk patients and optimize their disease management. The work performed in this thesis included longitudinal analysis of a cohort of patients diagnosed with acute audiovestibular hypofunction and of another cohort of age-related hearing loss patients, analyzing the link between vascular risk and cardiocerebrovascular disease.

Thus, the aims of this work are to assess if sudden sensorineural hearing loss (SSNHL), acute unilateral peripheral vestibulopathy (AUPVP), and acute unilateral audiovestibular hypofunction (AUAVH) can be associated with a higher prevalence of cardiocerebrovascular disease (CCVD) and CVRFs, and if vascular risk can be associated to age-related hearing loss and influence its severity.

First, a systematic review was performed including 805 patients from 11 AUPVP studies. The results were summarized regarding hemodynamic events, inflammation markers, and CVRFs in AUPVP. Dysfunctions in vertebrobasilar circulation and arterial stiffness, inflammatory and thrombotic events neutrophil-mediated and CVRFs were linked to AUPVP.

Secondly, a systematic review with meta-analysis from 102292 patients added that hypertriglyceridemia and hypercholesterolemia were independent risk factors from SSNHL.

From a group of 125 consecutive patients with SSNHL, AUPVP, or AUAVH and 250 age and sex-matched controls, a higher prevalence of CVRFs [diabetes mellitus (DM), high blood pressure (HBP) and dyslipidemia (DLP)] was verified in patients ($p<0.05$). A significantly elevated risk of acute unilateral inner ear hypofunction (AUIEH) was found in patients with two or more CVRFs [adjusted Odds Ratio (OR) 5.11]. Previous CCVD individually predicted AUIEH (OR 8.41). Subgroup analysis showed the same tendency in AUPVP and SSNHL.

Age-related hearing loss (ARHL) patients (n=156) were evaluated for vascular risk through personnel history of HBP, DM, or DLP. A low-frequency audiometric notch in 250 Hz or 500 Hz verified in 36 patients was significantly associated with the presence of HBP or DM or DLP (OR 3.54, $p<0.001$). Averaged hearing thresholds between 250 and 1000 Hz > 25 dB HL were associated with DM (OR 2.97, $p=0.032$). In conclusion, there are indirect evidence for vascular mechanisms in AUPVP, without significant populations sizes and control group, which was optimized with the presented case-control study. Hypertriglyceridemia and hypercholesterolemia may be independent risk factors for SSNHL. A diagnostic standardization in patients with SSNHL is needed regarding cardiovascular comorbidities. Low-frequency audiometric notches may be a possibility for vascular risk prediction in ARHL patients that merits future attention in larger populations studies.The risk factors may be well investigated to develop more evidence on etiologic incidents. If future studies show that these patients may reveal unknown vascular risks, this will have important implications for therapeutic and preventive strategies.

Keywords: Acute unilateral peripheral vestibulopathy, Sudden sensorineural hearing loss, Acute unilateral audiovestibular hypofunction**,** Cardiovascular risk factors, Age-related hearing loss

Resumo

O diagnóstico diferencial das patologias auditivas e vestibulares agudas é diverso, incluindo infeções virais, tumores, auto-imunidade entre outros. A associação destes eventos agudos com factores de risco cardiovascular (FRCV) e eventos vasculares tem sido analisada, existindo a suspeita de que alguns destes casos possam ser, na verdade, manifestações iniciais de patologia vascular trombótica ou hemorrágica da circulação de tipo terminal do ouvido interno. A crescente acuidade diagnóstica da imagiologia médica permitiu identificar hemorragias do ouvido interno e enfartes vestíbulococleares em eventos otológicos agudos. Analisar as potencias relações entre os eventos audiovestibulares agudos e o risco cardiovascular permitirá a identificação de eventuais doentes de alto risco e modificar a abordagem diagnóstica e eventualmente terapêutica destes casos. O trabalho realizado nesta tese consistiu na análise longitudinal de um grupo de doentes com perdas audiovestibulares agudas e um outro grupo de doentes com presbiacusia, analisando a associação com o risco cardiovascular e doença cardiocerebrovascular (DCCV).

Assim, os objectivos deste trabalho são avaliar se a ocorrência de surdez súbita neurossensorial (SSSN), hipofunção vestibular periférica aguda (HVPA) e hipofunção audiovestibular periférica aguda (HAVPA) poderão estar associadas a eventos cardiocerebrovasculares, avaliar uma possível ligação clínica entre FRCV e as perdas audiovestibulares agudas, e identificar possíveis associações entre o perfil de risco vascular e presbiacusia.

Numa etapa inicial avaliou-se qualitativamente a evidência presente na literatura num grupo final de 805 doentes de 11 estudos abordando a HVPA. Os resultados foram recolhidos relativamente a eventos hemodinâmicos, marcadores inflamatórios e FRCV na HVPA. Anomalias na circulação vertebrobasilar e rigidez arterial, modificações inflamatórias e trombóticas mediadas por neutrófilos e alta prevalência de FRCV foram associadas à HVPA. Em relação à SSSN, uma revisão sistemática com meta-análise já foi viável pela quantidade de dados existentes, incluindo 102292 doentes. Esta avaliação permitiu adicionar à literatura previamente existente a hipertrigliceridémia e a hipercolesterolémia como factores de risco independentes para a ocorrência de SSSN.

Na análise de doentes consecutivos com perda audiovestibular aguda , foram incluídos 125 indivíduos com SSSN, HVPA e HAVPA, e 250 indivíduos controlo emparelhados por idade e sexo. Foram analisadas as prevalências de hipertensão arterial (HTA), diabetes mellitus (DM) e dislipidémia entre grupos, estabelecendo uma comparação do risco vascular. Além disso, foi avaliada a existência de DCCV em cada grupo. Uma maior prevalência de FRCV foi verificada no grupo de doentes ($p<0.05$). O risco de perda audiovestibular aguda foi significativamente superior nos doentes com 2 ou mais FRCV (*adjusted Odds Ratio* (OR) 5.11). A história prévia de DCCV foi predictora da ocorrência de perda audiovestibular aguda (OR 8.41). A análise dos subgrupos (SSSN, HVPA e HAVPA) revelou a mesma tendência.

No grupo de 156 doentes com presbiacusia, o risco vascular foi avaliado mediante a história prévia de HTA, DM ou dislipidémia. Através da análise das curvas audiométricas individuais foi estudada a possível associação entre risco vascular e gravidade e tipo de curva audiométrica. Verificou-se a associação entre a presença de um entalhe audiométrico nas baixas frequências (250 ou 500 Hz) e a presença de pelo menos um FRCV (HTA, DM ou dislipidemia, OR 3.54, $p<0.001$). Além disso, limiares auditivos médios entre 250 e 1000 Hz > 25 dB HL estiveram associados com a presença de DM (OR 2.97, $p<0.05$).

Em conclusão, analisando qualitativa e quantitativamente a literatura existente, a evidência para mecanismos vasculares na HVPA existe, mas de forma indirecta, faltando estudos com população significativa e respectivo grupo controlo, o que se procurou completar com o presente trabalho. No que diz respeito à SSSN, os resultados deste trabalho revelam que a hipertrigliceridémia e a hipercolesterolémia podem ser factores de risco independentes para a ocorrência de SSSN. De facto, analisando a coorte do presente trabalho, os FRCV e a DCCV estiveram significativamente associados a perda áudio-vestibular aguda. Na presença de presbiacúsia, a observação de um entalhe audiométrico nas baixas frequências (250 ou 500 Hz) pode ser predictor de um maior risco vascular. Deste modo, a exploração diagnóstica nestes doentes poderá ser optimizada com eventuais repercussões na estratégia terapêutica a seguir.

Palavras Chave: Surdez súbita neurossensorial, Hipofunção vestibular periférica aguda, Hipofunção audiovestibular periférica aguda, Factores de risco cardiovascular, Presbiacusia

Purposes

The overall goal of this thesis was to evaluate if acute unilateral inner ear hypofunction (AUIEH) and age-related hearing loss (ARHL) are linked to vascular risk and how they could influence disease severity.

To hypothesize primary and secondary purposes, two research questions have been defined according to identified gaps in the literature:

1. Are sudden sensorineural hearing loss (SSNHL), acute unilateral peripheral vestibulopathy (AUPVP), and acute unilateral audiovestibular hypofunction (AUAVH) associated with higher vascular risk?
2. Does vascular risk influence the pattern of ARHL and its severity?

The primary purposes of the thesis were:

1. To perform a systematic review of the most recent evidence studying the links between AUPVP and vascular disease, exploring if AUPVP patients have a higher vascular risk than the general population;
2. To perform a systematic review and meta-analysis of case-control and cohort studies to determine if SSNHL patients have an increased cardiovascular risk;
3. To assess the cardiovascular risk factors (CVRFs) and vascular events in a population with AUIEH, including acute isolated vestibular or auditory loss and global inner ear hypofunction. The primary outcome is to evaluate the prevalence of three modifiable CVRFs [high blood pressure (HBP), Diabetes Mellitus (DM), or dyslipidemia (DLP)] in AUIEH compared to controls and the influence of the number of CVRFs in AUIEH occurrence. The secondary outcome is to compare patients' and controls' previous history of cardiocerebrovascular disease (CCVD).

The secondary purpose of this thesis is to assess the CVRFs and vascular events in a population diagnosed with ARHL and to explore if these factors can influence the severity of hearing loss and the type of audiometric data in the same source population to fill the identified gaps in the literature.

To achieve these goals, the inclusion criteria were the following:

1. Age over 18 years old;

2. Patients diagnosed with AUPVP, SSNHL, or AUAVH 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, initial and follow-up vestibular testing if vestibular symptoms were present [videonystagmography (VNG), video head-impulse test (vHIT)]. High blood pressure was defined when patients were taking antihypertensive medications, if their systolic blood pressure was 140 mmHg or more, or if their resting diastolic blood pressure was 90 mmHg or more. 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 non-fasting 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. 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 three days [5]. Acute unilateral vestibular hypofunction patients were diagnosed when the following full criteria were present: 1) acute vertigo lasting for at least 24 hours, (2) absence of auditory complaints, (3) horizontal unidirectional nystagmus present during physical examination, (4) lack of neurological symptoms or signs and (5) evidence of vestibular deficit was observed by vHIT. Acute unilateral audiovestibular hypofunction was diagnosed when patients had both vestibular hypofunction and acute sensorineural hearing loss without another identifiable origin;

3. Patients diagnosed with ARHL from July 2021 to July 2022. High blood pressure was defined when patients were taking antihypertensive medications, if their systolic blood pressure was 140 mmHg or more, or if their resting diastolic blood pressure was 90 mmHg or more. 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 non-fasting 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. 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.

Thesis Outline

This thesis is organized in four main parts, whose content is summarized below.

Part I is a general introduction to the thesis, giving an overview of the state of the art in the association between inner ear hypofunction and vascular risk.

Part II of this thesis contains four scientific papers, three published and one submitted for publication in international peer-reviewed journals with impact factor (Web of Science Core Collection):

- **Article 1:** Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review
- **Article 2:** Cardiovascular risk and sudden sensorineural hearing loss: a systematic review and meta-analysis
- **Article 3:** Cardiovascular risk factors among patients with acute unilateral inner ear hypofunction: a case-control study
- **Article 4:** Audiometric patterns and vascular risk in age-related hearing loss

Part III of the thesis provides a section with additional results complementing the main results with an analysis of the influence of cardiovascular risk on the caloric deficit in AUPVP and on the degree of hearing loss or hearing loss curve in SSNHL.

The supplements include a list of presentations given in this research field, the Prospero registration and the online supplement of “Cardiovascular risk and sudden sensorineural hearing loss: a systematic review and meta-analysis“.

This section also comprises mandatory documents necessary for this thesis's completion, namely Ethic Committee’s approvals (Supplement 1 and 2).

Introduction

The temporal bone interfaces with multiple intracranial and extracranial regions. Its anatomy reflects its essential role in embryology and in the trajectory of vessels, nerves, and pathogens through these regions. Understanding this anatomy is mandatory to explore the etiology and the safe and effective treatment of diseases of the inner ear.

The inner ear is locked within the temporal bone. The two inner-ear organs are incessantly at work. They have connections with the extraocular, cervical, trunk, and limb muscles, and they support a wide range of tasks, from stabilizing visible images on the retina to maintaining balance during the vast movements of the human body. Moreover, they constantly receive auditory inputs. Thus, the vestibulocochlear system is responsible for hearing and balance.

The vestibulocochlear system is in the interior of the petrous part of the temporal bone. It is composed of two organs with different functions but with similarities in functionality and structure: the auditory region, which include the external ear, middle ear, and anterior portion (cochlear) of the labyrinth, and the vestibular part at the posterior portion of the inner ear. The transmission of the nervous impulse from the cochlea is the function of the cochlear nerve, and the information from the posterior labyrinth is transmitted by the superior and inferior vestibular nerves. These three nerves constitute the VIII cranial nerve, the vestibulocochlear nerve (1).

The development of the vestibulocochlear system begins at the 4^{th} week of gestation, with the origin of the inner ear, from the otic placode (thickening of the ectoderm on the outer surface of the developing embryo), which invaginate in the otic mesenchyme and origin the otic vesicle. This last structure will develop the sacculus, the cochlear canal, the utriculus, and the semicircular canals. The membranous labyrinth originates from the otic capsule.

The inner ear is constituted by an osseous portion (bone labyrinth) and a membranous portion (membranous labyrinth). The last one has endolymph in its interior and is surrounded by another fluid, the perilymph, between the osseous and the membranous labyrinth (1,2). The bony labyrinth (from mesodermic origin) contains the vestibule (in the center), the semicircular canals (anterior, posterior, and lateral, in the posterior part), and the cochlea in the anterior part. The vestibule and the semicircular canals constitute the posterior labyrinth

responsible for the body balance, and the anterior labyrinth (cochlea) is dedicated to auditory function.

The membranous vestibule has two vesicles, the utriculus and the sacculus, the otolithic organs. The utriculus is bigger and occupies most of the superior part of the vestibule, with an ovoid form. The sacculus, with a spheric form, is inferior and smaller and is connected with the cochlear duct through the ductus reuniens. The sensory cells are in the macula, which can detect the body's linear accelerations in the horizontal plane (utriculus) and in the vertical plane (sacculus).

The three membranous canals are in the same plane as the bone canals with a ¼ of the diameter of their corresponding bone canal. They open in the utriculus, and the ampullary end of each canal has an ampullary crest with sensory cells, which are sensors for the body's angular accelerations. The vestibular nerve originates from the five sensory regions of the posterior labyrinth (two maculas and three ampullary crests).

Vertigo is a sensation that appears when the balance mechanism is disturbed. The balance is the function that allows the maintenance of the gravity center inside the polygon of sustentation during movement and at rest. Moreover, it enables the stability of the visual field (1). The vestibular nervous fibers that enter the brainstem end in the vestibular nuclei, which are connected with:

- Oculomotor nerves nuclei (III, IV, VI) through the longitudinal medial fascicle for visual field stabilization;
- Motoneurons of the anterior grey matter of the spinal cord through the vestibule-spinal fascicles for posture adaptation to balance alterations;
- Vagus nuclei for neurovegetative function control;
- Cerebellum through vestibular-cerebellum fibers for motor coordination;
- Thalamus and cerebral cortex through vestibular-thalamic and vestibular-cortical fibers for conscious perception of body movements and spatial orientation.

In conclusion, the ear is responsible for balance maintenance with vision, proprioception, and the cerebellum. The last one allows an unconscious muscular and posture control through the received inputs from the three other afferents.

The cochlear canal is situated inside the bony labyrinth and is a spiral canal with its origin in the vestibule and ending in the helicotrema. The cochlear canal has three walls:

1. Inferior, tympanic wall – composed of the basilar membrane supporting the spiral organ;

2. Superior, vestibular wall – formed by the vestibular membrane, which separates the cochlear canal from the vestibular scala;

3. External wall – includes the spiral ligament and the *stria vascularis*.

Epithelial structures on the basilar membrane form the spiral organ.

The cells of the spiral organ have synapses at the base with nerve fibers. The inner hair cells (IHC) (3500 cells and each one with 50 to 60 stereocilia) transform mechanical waves in nervous impulses. The outer hair cells (OHC) (12000 cells and each one with 100 stereocilia) have a protein (prestin) that is contractile and permits sound perception, reacting to specific frequencies (1,2).

The OHC have the function of adapting the cochlear responses to the different frequencies allowing better action of the IHC. The stereocilia of the OHC start contractions of the OHC which in turn leads to an increase in the amplitude of the movements of the basilar membrane. This phenomenon allows the contact between the IHC and the tectorial membrane with their depolarization and the transformation of the sound signal into an electric signal (1).

The inner ear is supplied by the labyrinthine artery (LA), an end artery (Fig. 1). Usually, the LA derives from the anterior inferior cerebellar artery (AICA) and gives two main branches, the common cochlear (CCA) and anterior vestibular (AVA) arteries. In the internal auditory canal, the LA runs on the anterior side of the VIII nerve, then, passing between the VIII and the VII nerves, it lies on the superior side of the cochlear nerve or in the furrow between the cochlear and the vestibular nerves. As it reaches the distal end of the canal and begins to divide into the labyrinthine branches, it lies in the lower area of the canal, between the cochlear and the vestibular nerves (3). Most of the branches of the LA supply the nerves, dura, and arachnoid of the canal and the bone (3).

The CCA divides into the main cochlear artery and the vestibulocochlear artery, forming the posterior vestibular and the cochlear artery. The apical three-fourths of the cochlea are supplied by the main cochlear artery and the basal one-fourth by the cochlear ramus. The vestibulocochlear artery enters the internal auditory canal and reaches the medial wall of the vestibule at the confluence with the basal turn of the cochlea. At this level, the vestibulocochlear artery divides into a cochlear branch for the modiolus and a vestibular branch in the direction of the posterior ampulla and the inferior part of the saccule (3).

The AVA supplies the utricle, superior part of the saccule, and ampullae of the superior and lateral semicircular canals. The artery follows the anterior side of the superior vestibular nerve to enter the inner ear through the superior cribrous area. After the branches to the nerve, the

superior wall of the saccule and the posterior wall of the utricle, the large utricular artery leaves the main stem. The anterior vestibular artery then divides into its terminal branches for the superior and the lateral canals (2,3). Thus, an overlap exists between inner ear vascular supply and inner ear innervation.

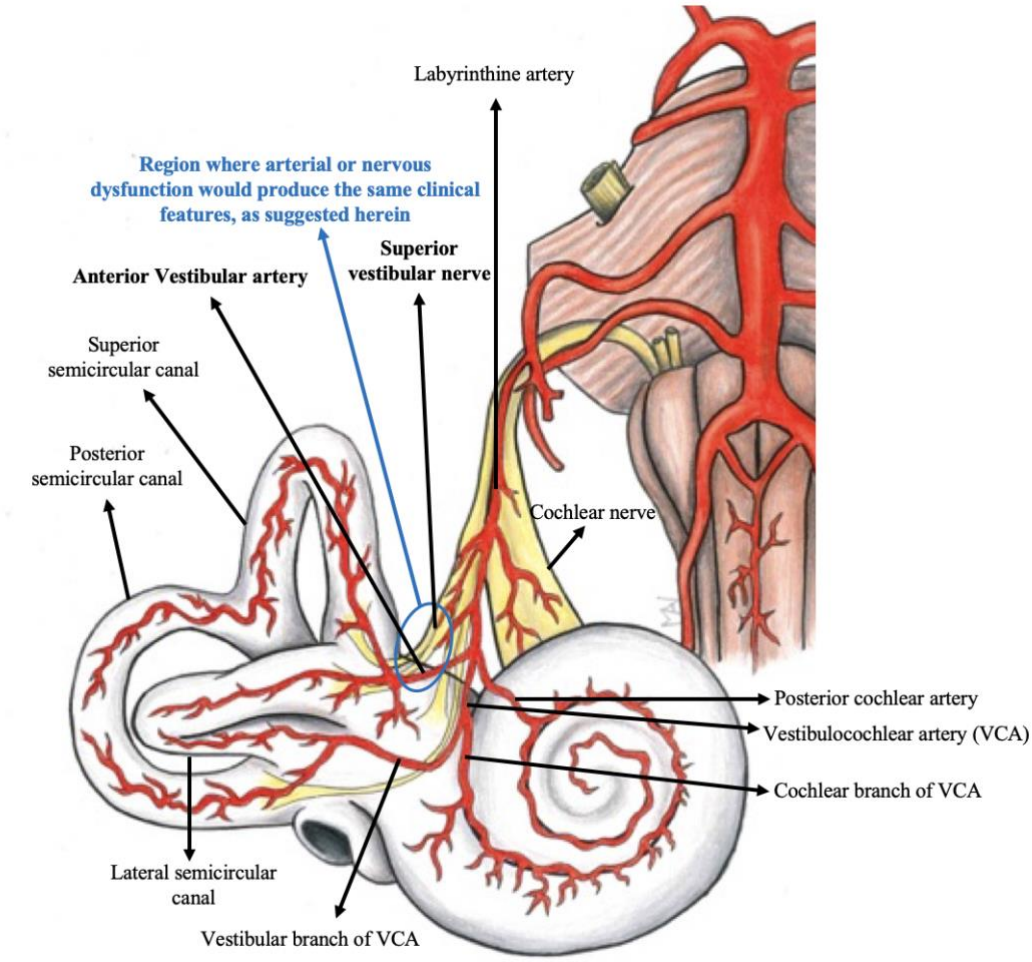

Figure 1. Inner ear vascular and nervous supply. (source: Mathilde Vercruysse, 2020)

The terminating spiral modiolar artery (SMA) is the main blood supplier to the cochlea; the SMA radiates over the scala vestibuli and across the spiral lamina. The two major capillary systems in the spiral ligament and stria derive from its branches to the lateral cochlear wall. These two capillary systems result in four distinct networks (4):

1. Arteriole system: The supra-strial capillary network of the spiral ligament. Above the attachment of Reissner's membrane, these microvessels are surrounded by a generous number of pre-capillaries. Location and arrangement suggest a plasma filter for the perilymph, but it was suggested that the perilymph might also originate in this region;

2. Venous system: The post-strial capillary network from radiating arterioles;

3. True capillary system: The ad-strial capillary network of the spiral ligament. Most of the capillaries in the middle part of the spiral ligament that pass behind the stria run a more or less straight downward course in the spiral ligament until they reach the floor of the outer sulcus;

4. The capillaries of the *stria vascularis*. The largest branches of the radiating arterioles enter the stria vascularis just below the attachment of Reissner's membrane, where they divide to form the strial network with its multiple anastomoses. The volume of cochlear blood flow (CoBF) is minimal, with CoBF estimated on the order of 1/1000000 of total cardiac output in humans (5).

The vessel walls of the pre-capillary and post-capillary vessels of the spiral ligament have smooth muscle cells which regulate lateral wall blood flow (6). On the other hand, the *stria vascularis* capillaries are highly specialized vascular epithelia with a minor role in blood flow regulation, but crucial in maintaining the endocochlear potential, ion transport, and endolymphatic fluid balance (4). Cochlear microcirculation is strongly auto-regulated (7-9). Indeed, an important decrease in systemic blood pressure will result in a slight change in CoBF, and an elevation does not correspondingly change it in the cerebrospinal fluid pressure (7). Moreover, rapid recovery of CoBF occurs during the occlusion of the AICA (7). Inner ear function requires an efficacious delivery of oxygen and glucose. Then, a well-regulated CoBF is crucial and is hypothesized to include local and central regulatory controls. This model states neural- and autocrine/paracrine-based regulation of vasoconstriction and dilation at the level of artery and arterioles and at the level of capillaries (7).

The vasodilation and neurotransmission in the mammalian cochlea may be mediated by nitric oxide (NO), soluble cyclase (sGC), and cyclic guanosine-monophosphate (GMP) (10,11). Indeed, NO and NO synthase (NOS) are present in various parts of the cochlea. Endothelial NOS (eNOS) was found in the spiral ligament, in the *stria vascularis*, in cells of the organ of Corti, in nerve fibers, in blood vessels of the lateral cochlear wall, and some perikaryia of the spiral ganglion (12). Inducible NOS (iNOS), which is faint or not present in the normal cochlea, has an important expression in pathological conditions such as endolymphatic hydrops (13), ischemia (14), ototoxicity (15), and aging (16). Sodium nitroprusside, a NO donor, was shown to elevate CoBF and deteriorate hearing ability (17).

On the other hand, the inhibition of NOS in the cochlea leads to a reduction of CoBF (18). Using guinea pigs, Nagura *et al*. (17) produced focal microcirculation disorders at the lateral wall of the cochlea. They assessed CoBF with and without pre-administration of *N* omega-

nitro-L-arginine methyl ester (L-NAME). Blood flow was significantly decreased around the disorder zone in the L-NAME pretreatment group compared to the control group. They reported that the "formation of endogenous NO plays a key role in maintaining CoBF in acute focal cochlear microcirculation disorder."

Theoretically, a sudden interruption of the blood flow of the anterior vestibular artery could affect the same structures of superior vestibular nerve inflammation, and the symptoms could be similar in the setting of an inflammatory or a vascular insult (20,21).

Like the inner ear, the kidney, heart and eye are supplied with an end artery, and many of the diseases that affect these organs are, in fact, mediated by vascular events. Indeed, it is widely accepted that their loss of function (sudden or chronic) can be due to inflammatory diseases, infections, toxic events, genetic causes, and vascular suffering (coronary disease and vascular kidney disease, for example). The same rationale may be applied to the inner ear end artery. In fact, the end artery at the inner ear could be more susceptible to lesions if we consider that there is recent evidence of functionally relevant anastomotic vessels, known as collateral arteries, which interconnect epicardial coronary arteries (22). This type of collateral vasculature is not known at the level of the inner ear.

Acute renal failure could result from hypovolemia, renal hypoperfusion, or glomerular disease (post-infectious, thrombotic microangiopathy, interstitial nephritis, **i**schemia, or toxins such as aminoglycosides and cholesterol emboli) (23).

At the heart level, the most common etiology of acute heart failure is cardiac ischemia, where (sub)-total coronary occlusion leads to decreased contractility in myocardium subtended by the affected coronary artery. Less common causes of acute cardiac dysfunction are non-ischemic myocardial insults, like viral and toxic drug-induced cardiomyopathy (24).

At the eye, a sensory organ like the inner ear, a transient visual loss lasting less than 24 hours can be caused by emboli (due to embolic occlusion of retinal, optic disc, and choroidal blood vessels). The emboli may often be visible on ophthalmoscopic examination, which highlights the principal difference between eye and inner ear examinations — the presence of an embolus warrants thorough vascular and cardiac evaluation (25).

Acute unilateral peripheral vestibulopathy is considered the third most common peripheral vestibular disorder after benign paroxysmal positional vertigo and Meniere's disease (26,27). Several hypotheses have been proposed for the etiology of AUPVP, but the exact mechanism remains unknown. Nowadays, the term AUPVP is preferred over "vestibular neuritis"

because it is unclear whether it is always an inflammation that provokes the dysfunction (22). However, until recently, most literature contains “vestibular neuritis” (VN). In this work, the term AUPVP will be used henceforth.

According to the literature, the most likely origin of AUPVP is viral, namely, herpes simplex type 1. This is supported by a genome-wide association study showing a link between the disease and the single nucleotide variants of the host factor for HSV 1 replication (23). Even though other etiologies have been suggested, including thrombosis and an autoimmune inner ear reaction (24).

The clinical picture varies according to the extent to which the vestibular end organs or their innervation are affected (25). The patient might present spontaneous horizontal nystagmus beating away from the lesion side and caloric testing paralysis/paresis; a reduced gain in the vHIT supports the diagnosis (22). Vestibular-evoked myogenic potentials (VEMPs) help distinguish between superior and inferior vestibular nerve involvement (28). Acute unilateral peripheral vestibulopathy appears more common in the superior vestibular labyrinth and its afferents, which could be explained by the longer and narrower path through its bony canal and also explains why the posterior semicircular canal and saccule are less affected (29). A previous history of upper airway infection or concomitant findings of herpes infection strongly points toward a viral etiology. However, not all patients fit this profile, and other causes may be considered, namely, a vascular etiology. Like the inner ear, the kidney, heart, and eye are supplied with an end artery. Many diseases that affect these organs are mediated by vascular events, a topic that consequently deserves further research in AUPVP (30-32). Any disturbance in the cochleovestibular blood supply can provoke an insult in the fluid homeostasis and metabolic supply and may be related to a variability of inner ear disorders, such as sudden deafness, autoimmunity, age-related hearing loss, AUPVP and Meniere’s disease (33).

A longitudinal population-based cohort study of 1925 individuals concluded that smoking, central adiposity, and poorly controlled diabetes mellitus predicted incident hearing impairment, which may suggest inner ear atherosclerotic events (34). Like other organs mentioned above, the labyrinth is also vulnerable to ischemia because it requires high-energy metabolism (2). By contrast, the retrocochlear acoustic nerve has an abundant collateral blood supply from the lateral medullary artery, adjacent dura mater and petrous bone arteries, and the inferior lateral pontine artery (2). Thus, the different parts of the inner ear may be more prone to ischemia than the nerves, considering the different patterns of vascular supply.

Sudden sensorineural hearing loss is defined as a decrease in hearing of ≥ 30 decibels (dB) affecting at least three consecutive frequencies within 72 hours or less (35). The estimated incidence is approximately 5-20 per 100,000/year, and the spontaneous recovery rate is 32–65% (36). Epidemiological surveys suggest an increasing incidence of SSNHL (37). Causal identification is found in only 10 to 30% of the cases without sufficient evidence (37,38). Several causes have been proposed, including infectious, autoimmune, vascular, metabolic, hematological, and neurological diseases. A recent history of upper airway infection or concomitant findings of viral infection also points towards a viral etiology, presumably the predominant cause. However, it does not account for all patients, and viral infections do not explain several features: steroid treatment does not necessarily resolve hearing loss, and antiviral therapy does not seem to affect disease outcomes (38). The inaccessibility of the inner ear to study SSNHL pathology makes it challenging to find an identifiable cause without harming hearing or vestibular function.

Atherosclerosis is accompanied by an autoimmune response to low-density lipoprotein cholesterol (LDL-c) and other antigens that causes ischemic heart disease, strokes, and peripheral vascular disease, collectively called cardiovascular disease (CVD) (39). Histopathological studies in the elderly with arteriosclerotic changes throughout the auditory system and a large longitudinal study of a middle-aged cohort showed that atherosclerosis was associated with a higher 5-year incidence of hearing impairment, showing that vascular events can affect the inner ear (40). Evidence indicates that traditional CVRFs like HBP, DM, and DLP may contribute to SSNHL (41-47). However, past reviews reported evidence until 2014. They did not report information from some CVRFs [high levels of triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and metabolic syndrome (MetS)] (41), issues that are addressed in the present work. It was also suggested that patients with SSNHL had a higher risk of developing future stroke (48,49), although SSNHL was not associated with future acute myocardial infarction (47,48).

Quaranta *et al.* reported signs of endothelial dysfunction in SSNHL. Fisch described the blood pressure dysregulation of the *stria vascularis* (a process related to age and CVRFs) as a consequence of cochlear atherosclerosis, in which the tunica adventitia loses fibroblasts and becomes thicker, which in turn leads to plasmatic viscosity and platelet aggregation (49-51). Consequently, vascular pathology is supposed to be an important etiological factor of SSNHL (52,53).

Acute unilateral inner ear hypofunction can be due to a global impairment of function (labyrinthitis/AUAVH) or a partial disorder, AUPVP or SSNHL.

As referred above, in SSNHL and AUPVP, previous upper airway infection or concomitant findings of viral infection point towards a viral etiology. However, the majority of patients do not have this profile. 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, auto-immunity, age-related hearing loss, and AUPVP (33).

Cardiovascular risk factors are divided into two major classes: non-modifiable (age, gender, and family history) and modifiable risk factors HBP, tobacco use, DM, physical inactivity, unhealthy diet, and DLP (34).

Various studies assessed CVRFs in AUPVP and SSNHL as individual and separated inner ear events. The study of CVRFs in AUIEH, considering that AUPVP and SSNHL might have common pathophysiological events, at least in some high vascular risk patients taking into account previous results, may add significant new findings regarding the understanding of acute inner ear diseases (42,47,54,55).

Age-related hearing loss or presbycusis is the hearing loss that results from the degenerative aging process. It is the most frequent sensory dysfunction in the elderly with an estimated prevalence between 25% and 80% (56). It induces impairment in speech perception, induce depression, and social isolation. It was observed that HBP and DM patients showed the greatest decrease in auditory thresholds when compared to other groups (57). Current research shows that ARHL is a multifactorial condition with multiple pathways that contribute to hearing loss (57). A link between ARHL, inflammation, and CVRFs was proposed. Chronic inflammation begins in an insidious and unnoticed manner, which is compatible with the temporal progression of ARHL. The role of inflammation in many diverse age-related diseases suggests that it is the main event in the physiology of aging. Lifestyle choices such as weight gain and smoking can contribute to high levels of chronic inflammation in the vascular system, which may be the underlying link in ARHL (57).

Friedland demonstrated a statistical relationship between audiometric patterns and the probabilities of developing a vascular disease (58,59) and Susmano *et al.* with 103 patients and 101 controls found that patients with ischemic heart disease (IHD) appear to manifest hearing loss up to eight times more frequently than those without IHD (60). He considers low-

frequency hearing loss an “early marker” of heart disease. Patients presenting audiometric patterns that correspond to greater probabilities of CCVD could then be identified. Additionally, there was a significant difference in audiometric thresholds between healthy subjects and those presenting HBP, cardiovascular symptoms, and transient ischemic attacks (61-66). Moreover, increasing evidence shows that decreased vascularization of the auditory system negatively affects hearing by *stria vascularis* dysfunction resulting in abnormal endolymph potentials (58).

Cochlear hair cells are stimulated by specific frequencies, with low frequencies at the apex and high frequencies in the basal turn. The *stria vascularis* is a highly vascularized cochlear region. Blood flow variations have an important influence on endolymph potential voltages, considering that vascular diameters vary through the different cochlear areas and that it can vary more in the apex region than in the basal turn (58,66). Then, the rationale of specific hearing loss frequencies corresponding to each area of disturbed CoBF could explain the different patterns in age-related hearing loss. When the endolymphatic potential is significantly reduced, the cochlea amplifier has a weaker performance. In animal models, an endolymphatic potential lower than 20 mV provokes “cochlea starving” (58). A short period of transient cochlear ischemia reduced endolymphatic potentials by up to 17.5 mV within 15 minutes (67). Lars-Göran and Hawkins demonstrated that the atrophy of the *stria vascularis* leads to a decreased vascularization of the cochlea that primarily affects the apical and basal segments. Then, the low endolymph voltage results in reduced hearing function in the low and high-frequency ranges (68).

Schuknecht defined four distinct types of ARHL based on pathologic findings in human temporal bones (69):

1. *Sensory ARHL*, hair cells are progressively lost, beginning at the base of the cochlea. Patients with this abnormal pattern tend to have steeply sloping high-frequency hearing losses;
2. *Neural ARHL* implies a loss of auditory nerve fibers; these patients tend to have reduced speech discrimination out of proportion to their pure tone thresholds;
3. *Stria/Metabolic ARHL* presents an atrophy of the *stria vascularis*, and these patients have relatively flat audiograms;
4. *Cochlear conductive* or *mechanical ARHL*. No light-microscopic abnormalities are seen in these specimens, and Schuknecht theorized that an age-related change in the stiffness of the basilar membrane resulted in hearing loss. These patients have gradually descending (approximately 25 dB/octave) pure tone thresholds.

However, it is considered that these patterns are not clinically practical because of the variability of audiometric shape and severity in individuals with ARHL, and the losses do not fall naturally into these patterns. Friedland considered the strial and low-sloping of interest for predicting vascular disease (58). To consolidate this hypothesis, the pathologies considered were myocardial infarction (MI), coronary artery disease (CAD), cerebrovascular accident (CVA), and transient ischemic attack (TIA). It is affirmed that the presence of subjects with none of the usual CVRFs but with a strial or low-sloping frequency hearing loss suggests a missing CVRF.

Red blood cell velocity (RBCv) and vascular permeability were previously tested in animal models (Fischer rats) to assess age-related differences in auditory sensitivity (70). These authors suggested that the most significant reduction in RBCv occurs before the development of auditory sensitivity loss. Thus, extended periods of reduced RBCv flow may be necessary to provoke progressive hearing loss, such as with presbycusis. More evidence evaluating the role of microvascular disease in ARHL was proposed by Liew G *et al.* (71). They assessed the link between retinal microvascular abnormalities and ARHL in a population-based study on 1511 older individuals. Interestingly, retinopathy in women was associated with hearing loss (adjusted odds ratio (OR), 2.10; 95% confidence interval (CI), 1.09-4.06) but not in men. The verified associations were stronger for worse low-frequency (0.25 to 1.0 kHz) hearing loss in women (adjusted OR, 3.00; 95% CI, 1.25-7.19) but were absent for high-frequency hearing loss. Accordingly, it was suggested the hypothesis that microvascular disease may play a role in ARHL in women, particularly in low-frequency hearing loss.

Considering all the arguments presented above, that certain risk factors, such as DM, HBP, and DLP are more prevalent in patients with CCVD and that the common factor among these CVRFs is the reduced vascularization, leading to the suboptimal blood supply to vital organs, a thesis purpose can be defined. The early identification of the vascular risk based on inner ear dysfunction could lead to an earlier diagnosis, allowing prevention and prompt treatment of CCVD.

Scientific Paper Number 1

Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review

João Simões, Stephan Vlaminck, Raquel Seiça, Frederic Acke, António Miguéis

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Review

Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review

Meccanismi vascolari nella vestibolopatia periferica acuta unilaterale: una revisione sistematica

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SUMMARY

Acute unilateral peripheral vestibulopathy (AUPVP) is a frequent cause of vestibular loss. Several aetiologies have been proposed, but the exact mechanism remains unknown. The aim of this study is a systematic analysis of the literature evaluating the vascular aetiology of AUPVP. A systematic literature search was performed in PubMed, Cochrane Library and Embase, including articles published from January 1st, 2010 to November 30th, 2020. Two reviewers independently selected articles investigating a link between AUPVP and vascular disease. The following information was extracted: year of publication, country, level of evidence, assessed vascular risk factors and number of patients. A total of 450 articles was obtained. Eleven articles were retained with 100% agreement between the two reviewers. In a pooled population of 805 patients, the main results were the higher neutrophil to lymphocyte ratio and higher prevalence of vascular risk factors among AUPVP patients. A meta-analysis was not performed because the studies were too heterogeneous in terms of methodology. Indirect arguments for vascular mechanisms in AUPVP were found. These findings indicate that larger prospective well-controlled studies are needed to clarify the vascular aetiology of AUPVP.

KEY WORDS: acute unilateral vestibulopathy, risk factors, vestibular neuritis, vascular, acute vertigo

RIASSUNTO

La vestibolopatia periferica unilaterale acuta (AUPVP) è causa frequente di perdita della funzione vestibolare. Sono state proposte diverse eziologie, ma il meccanismo esatto rimane sconosciuto. Lo scopo di questo studio è condurre un'analisi sistematica della letteratura per valutare l'eziologia vascolare dell'AUPVP. Una ricerca sistematica della letteratura è stata eseguita mediante PubMed, Cochrane Library ed Embase, includendo articoli pubblicati dal 1 gennaio 2010 al 30 novembre 2020. Due revisori hanno selezionato in modo indipendente articoli che studiano un collegamento tra AUPVP e malattie vascolari. Sono state estratte le seguenti informazioni: anno di pubblicazione, paese, livello di evidenza, fattori di rischio vascolare valutati e numero di pazienti. In totale sono stati identificati 450 articoli. Tra questi sono stati considerati gli undici su cui vi era completo accordo fra i due revisori. In una popolazione aggregata di 805 pazienti, i risultati principali sono stati il più alto rapporto tra neutrofili e linfociti e la maggiore prevalenza di fattori di rischio vascolare tra i pazienti con AUPVP. Non è stata eseguita una meta-analisi perché gli studi erano troppo eterogenei per quanto riguarda la metodologia. Sono stati trovati argomenti indiretti per i meccanismi vascolari in AUPVP. Questi risultati indicano che sono necessari studi prospettici più ampi e ben controllati per chiarire l'eziologia vascolare in AUPVP.

PAROLE CHIAVE: *vestibolopatia unilaterale acuta, fattori di rischio, neurite vestibolare, vascolare, vertigini acute*

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Introduction

Acute unilateral peripheral vestibulopathy (AUPVP) is considered the third most common peripheral vestibular disorder after benign paroxysmal positional vertigo and Meniere's disease [1,2]. Several hypotheses have been proposed for the aetiology of AUPVP, but the exact mechanism remains unknown. Nowadays, the term AUPVP is preferred over "vestibular neuritis" because it is unclear whether it is always an inflammation that provokes the dysfunction [3]. However, until recently, the vast majority of the literature contains the term "vestibular neuritis" (VN). In this work, the term AUPVP will be used henceforth.

According to the literature, the most likely origin of AUPVP is viral, namely herpes simplex type 1. This is supported by a genome wide association study showing a link between the disease and single nucleotide variants of the host factor for HSV1 replication [4]. However, other aetiologies have been suggested including thrombosis and an autoimmune inner ear reaction [5].

The clinical picture varies according to the extent to which the vestibular end organs or their innervation are affected [6]. The patient might present a spontaneous horizontal nystagmus beating away from the lesion side and caloric testing paralysis/paresis; a reduced gain in the video head impulse test (vHIT) supports the diagnosis [3]. Vestibular-evoked myogenic potentials (VEMPs) are helpful to distinguish between involvement of the superior and inferior vestibular nerves [7]. Acute unilateral peripheral vestibulopathy appears to be more common in the superior vestibular labyrinth and its afferents, which could be explained by the longer and narrower path through its bony canal and also explains why the posterior semicircular canal and saccule are less affected [8]. A previous history of upper airway infection or concomitant findings of herpes infection strongly points towards a viral aetiology. However, not all patients fit this profile and other causes may be considered, namely a vascular aetiology. Actually, like the inner ear, the kidney, heart and eyes are supplied with an end artery and many of the diseases that affect these organs are, in fact, mediated by vascular events, a topic that consequently deserves further research in AUPVP [9-11]. Any disturbance in the cochleovestibular blood supply can provoke an insult in the fluid homeostasis and metabolic supply, and may be related to a variability of inner ear disorders, such as sudden deafness, autoimmunity, age-related hearing loss, AUPVP and Meniere's disease [12].

The inner ear is supplied by the labyrinthine artery (LA), an end artery. Usually, the LA derives from the anterior inferior cerebellar artery (AICA) and gives two main branches, the common cochlear (CCA) and anterior vestibular (AVA) arteries. The CCA divides into the main cochlear artery and the vestibulocochlear artery, the latter forming the posterior vestibular and the cochlear artery. The apical three fourths of the cochlea are supplied by the main cochlear artery and the basal one by the cochlear ramus. The AVA supplies the utricle, superior part of the saccule and ampullae of the superior and lateral semicircular canals. In contrast, the posterior vestibular artery supplies the inferior part of the saccule and the ampulla of the posterior semicircular canal [13]. Thus, an overlap exists between inner ear vascular supply and inner ear innervation. Theoretically, a sudden interruption of the blood flow of the anterior vestibular artery could affect the same structures of a superior vestibular nerve inflammation, and the symptoms could be the same in the setting of an inflammatory or a vascular insult [14]. A longitudinal population-based cohort study of 1925 individuals concluded that smoking, central adiposity and poorly controlled diabetes mellitus predicted incident hearing impairment, which may suggest inner ear atherosclerotic events [15]. The labyrinth is also vulnerable to ischaemia, like the other organs mentioned above, because it requires high-energy metabolism [13]. By contrast, the retrocochlear acoustic nerve has an abundant collateral blood supply from the lateral medullary artery, arteries of the adjacent dura mater and petrous bone and the inferior lateral pontine artery [13]. Thus, the different parts of the inner ear may be more prone to ischaemia than the nerves considering the different patterns of vascular supply.

In this work, we performed a systematic review of the most recent evidence studying the links between AUPVP and vascular disease, exploring if AUPVP patients have a higher vascular risk than general population.

Materials and methods

Identification and selection of studies

A systematic review was performed in December 2020 using three electronic databases: 1) PubMed, 2) the Cochrane Library and 3) Embase. The search strategy is presented in Table I. Studies published in English between January 1st, 2010 and November 30th, 2020 were retrieved.

The term VN was used also considering that the majority of published studies regarding AUPVP use this nomenclature. The literature search, selection and analysis were independently performed by two researchers (JS and AM). The studies included in our review were eligible if they met the following inclusion criteria: 1) studies in Humans, 2) definition of AUPVP clearly stated, 3) studies investigating a link between AUPVP and vascular disease and 4) one of the following types of articles: prospective cohort studies of consecutive patients, case-control studies of consecutive

Table I. Search strategy.

PubMed	(Vertigo[Other Term]) AND (risk factors[MeSH Terms]); (vertigo[Other Term]) AND (vascular[Other Term]); (acute vestibular neuritis[MeSH Terms]) AND vascular; (acute vestibular neuritis[MeSH Terms]) AND (risk factors[MeSH Terms]); (dizziness[MeSH Terms]) AND (risk factors[MeSH Terms]); (dizziness[MeSH Terms]) AND (vascular[Other Term])
Embase	((acute unilateral peripheral vestibulopathy) OR (vestibular neuritis)) AND ((risk factors) OR (vascular))
Cochrane	*(vestibular loss) OR (vestibular neuritis) OR (vestibular hypofunction)ti,ab,kw*

patients, retrospective reviews of consecutive patients and selected case series (prospective or retrospective). Studies were excluded if they consisted of expert opinions, reviews, letters or comments, original studies with different themes of interest, experiments on animals or cadavers and in vitro studies. The article selection was performed according to the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Fig. 1) [16]. All the discrepancies between researchers were resolved by consensus. The following information of the included studies was recorded: author, year of publication, country of publication, level of evidence, number of patients with AUPVP and analysed cardiovascular risk factors (CVRFs). Other papers were used to contextualise and discuss the presented studies.

Level of evidence

The included articles were evaluated with a level of evidence based on the Oxford Centre for Evidence-Based Medicine [17]. Level 1a refers to a systematic review of randomised controlled trials, level 1b to an individual RCT, level 2a to a systematic review of cohort studies, level 2b to an individual cohort study/low-quality RCT, level 3a to a systematic review of case-control studies, level 3b to an individual case-control study, level 4 to a case-series or poor-quality cohort/case-control study, level 5 to a case report or expert opinion. An independent assessment was carried out by the two reviewers. In case of disagreement, a third reviewer was consulted and consensus was stablished.

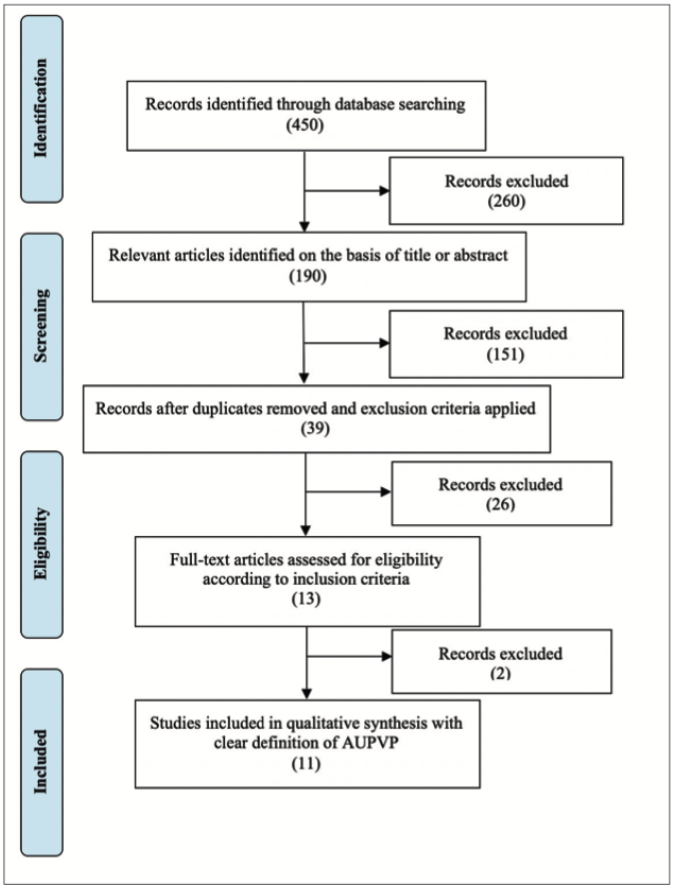

Figure 1. PRISMA flow diagram.

Results

General results

A total of 450 records were identified in the initial search. After identifying relevant articles based on title or abstract, 190 papers were retained, of which 151 were removed after application of exclusion criteria and elimination of duplicates. Then, the full text was read to confirm the eligibility of the articles according to the inclusion criteria. Twenty-six articles were further excluded. Two studies were eliminated due to absence of clear definition of AUPVP. Finally, 11 articles met all inclusion criteria. This selection process is presented in Figure 1. The final selection of studies had an interobserver agreement of 100%. The heterogeneity of the selected studies and different methodologies made meta-analysis with pooled comparability impossible.

Level of evidence

Five studies were attributed with level 3b of evidence and 6 studies with level 4. The agreement between reviewers regarding the level of evidence was achieved for 9 studies. A third observer was needed to judge 2 studies and, after discussion, 100% of agreement was obtained.

Study characteristics

The total AUPVP population of the 11 studies was 805 adults aged 18-92 years. Nine studies had a gender-bal-

anced population [18-26]. One study had a small number of females [27] and another did not provide data regarding gender distribution [28].

Details of the included articles are shown in Table II and III regarding included patients, nomenclature, measured outcomes and main results.

Studies investigating haemodynamic dysfunction in AUPVP

One of the proposed mechanisms for acute vestibulopathy is embolic labyrinthine infarction. Labyrinthine infarction can be diagnosed only in association with other infarctions involving the brainstem or cerebellar areas supplied by the anterior inferior cerebellar artery, because current imaging techniques cannot visualise an infarction confined to the labyrinth [27]. Of 10 patients with acute audiovestibulopathy, 3 had isolated unilateral vestibulopathy. The embolic labyrinthine infarction was diagnosed based on the presence of cardiac or artery-to-artery sources of embolism and concurrent embolic infarctions observed in the non-AICA territories [27]. One patient had an atrial fibrillation, one an unknown patent foramen ovale and the other presented an occlusion of the vertebral artery. All 3 patients had concomitant infarctions on MRI, but only peripheral vestibular symptoms. None of the patients presented MRI findings in the involved labyrinth.

The vertebral artery hypoplasia (VAH) was also proposed

Table II. Summary of the definition of AUPVP (definition of cases) in each study included.

First author / year	Definition of cases	Terms used
Adamec I, 2015 [18]	Vertigo attack lasting no more than 48 h, spontaneous horizontal-torsional nystagmus with the fast phase towards one side, positive head-thrust test to the other side and absence of skew deviation, a normal brain CT scan	Vestibular neuritis
Chuang YM, 2011 [19]	Acute vertigo, nausea and postural imbalance; unilateral deficit of the horizontal semi-circular canal and caloric irrigation showed > 25% canal paresis of the affected ear, a horizontal spontaneous nystagmus with a rotational component towards the unaffected ear (fast phase) and the head-thrust test showed an ipsilateral deficit of the horizontal canal, no hearing symptoms and exclusion of other vestibular dysfunction	Vestibular neuropathy
Chuang YM, 2011 [20]	Acute onset of rotatory vertigo, nausea and postural imbalance; unilateral deficit of the horizontal semi-circular canal and caloric irrigation showed > 25% canal paresis of the affected ear, a horizontal spontaneous nystagmus with a rotational component towards the unaffected ear (fast phase) and the head-thrust test showed an ipsilateral deficit of the horizontal canal, no tinnitus or acute hearing loss and exclusion of central, bilateral or other peripheral vestibular dysfunction	Vestibular neuropathy
Chung JH, 2017 [21]	Acute vertigo lasting for at least 24 hours, absence of auditory complaints, horizontal unidirectional nystagmus present during physical examination, and absence of neurological symptoms or signs	Vestibular neuritis
Han W, 2018 [22]	Strong vertigo attacks, vertigo attack no > 72 h; spontaneous horizontal-torsional nystagmus with the fast phase towards one side; obvious loss of vestibular function as indicated by the video head impulse test; and absence of auditory complaints and neurological symptoms or signs	Vestibular neuritis
Liqun Z, 2018 [27]	Acute peripheral vestibular syndrome with spontaneous horizontal-torsional nystagmus beating toward the nonaffected side and vestibular deficit in VHIT or caloric test	Unilateral peripheral vestibulopathy
Navari E, 2019 [23]	Long-lasting vertigo (> 12 h) that was not attributed to other causes screened with HINTS plus, vestibular deficit in VHIT, caloric test and VEMPS	Acute unilateral vestibulopathy
Oh EH, 2020 [24]	Acute peripheral vestibular syndrome with spontaneous horizontal-torsional nystagmus beating toward the nonaffected side and vestibular deficit in VHIT or caloric test	Acute unilateral vestibulopathy
Oron Y, 2017 [25]	Acute vertigo lasting for at least 24 hours, absence of auditory complaints, horizontal unidirectional nystagmus present during physical examination, and absence neurological symptoms or signs	Vestibular neuritis
Şahin Mİ, 2019 [26]	Acute vertigo, nausea, vomiting, postural instability, horizontal spontaneous nystagmus with a rotational component, and absence of hearing loss and other neurologic signs	Vestibular neuritis
Uffer DS, 2016 [28]	Patients with prolonged acute vertigo and nystagmus without hearing loss, for which no other diagnosis or more likely cause was found	Acute unilateral peripheral vestibulopathy

VHIT: video head impulse test; VEMPs: vestibular-evoked myogenic potentials; HINTS: head-impulse, nystagmus, test-of-skew.

Table III. Overview of the study included.

First author / year	Level of Evidence	Outcome Measured	No. of patients	Mean age of patients (years, range)	Vascular risk factor	Gender	Summary of results	Country
Adamec I, 2015 [18]	4	AUPVP cases in seasons; vascular risk factors	79	52.3 (20-86)	Hypertension, diabetes mellitus, hyperlipidaemia	41 male 38 female	No evidence of seasonality of AUPVP. Significant proportion of patients older than 50 years who had vascular risk factors	Croatia
Chuang YM, 2011 [19]	3b	Vertebral artery hypoplasia	69	52.8 (27-82)	Haemodynamic effect of the vertebral artery hypoplasia on the vestibular labyrinth	29 male 40 female	Vertebral artery hypoperfusion may impede blood supply, contributing to the development of AUPVP	China
Chuang YM, 2011 [20]	3b	Vestibular paresis	69	52.8 (27-82)	Effect of vertebral artery hypoplasia on prognosis of AUPVP	29 male 40 female	Comorbid vertebral artery hypoperfusion may predispose to severe AUPVP at acute stage	China
Chung JH, 2017 [21]	3b	Arterial stiffness	58	53.8 (NA)	Arterial stiffness and MetS	25 male 27 female	Arterial stiffness and higher metabolic syndrome scores are associated with the development of AUPVP	Korea
Han W, 2018 [22]	3b	Cerebrovascular risk factors	90	43.62 (27-92)	Age, hypertension, diabetes mellitus, lipids, carotid plaques	44 male 46 female	Prevalence of carotid plaque was significantly higher in AUPVP patients than in healthy controls. No differences regarding hypertension, diabetes mellitus and lipids	China
Liqun Z, 2018 [27]	4	Layrinthine infarction	10	57.2 (38-76)	Embolic source	8 male 2 female	Three patients developed AUPVP without evidence of auditory involvement. Embolic sources should be sought in patients with acute audiovestibulopathy of unknown aetiology	China
Navari E, 2019 [23]	4	Recovery rate and need of rehabilitation	59	Male 54.06 (24-77) Female 58.31 (23-81)	Age	31male 28 female	No effects of age in spontaneous recovery and in need of vestibular rehabilitation after AUPVP	Italy
Oh EH, 2020 [24]	3b	Gene expression NLR	10 72	60.2 (40-84) 60.6 (NA)	Inflammation	6 male 4 female 39 male 33 female	The neutrophil-mediated immune pathway may contribute to the development of AUPVP by mediating inflammatory and thrombotic changes in the vestibular organ	Korea
Oron Y, 2017 [25]	4	Vascular risk	160	56.22 (18-89)	Dyslipidaemia, obesity, diabetes mellitus, hypertension, ischaemic heart disease	64 male 96 female	A significantly higher prevalence of vascular risk factors was found among AUPVP hospitalised patients in comparison to the general population	Israel
Şahin Mİ, 2019 [26]	4	NLR and PLR	104	44 (18-71)	Inflammation	53 male 51 female	The elevations of NLR and PLR support the role of inflammation in AUPVP. The high level of mean platelet volume indicates the possible role of the vascular thrombosis in the etiology of AUPVP	Turkey
Uffer DS, 2016 [28]	4	Vestibular lesions patterns	25	NA (18-80)	NA	NA	The results do not support the neuritis hypothesis since about 3/4 of the patients had an intralabyrinthine lesion pattern inconsistent with an isolated nerve lesion	Switzerland

AUPVP: acute unilateral peripheral vestibulopathy; MetS: metabolic syndrome; NLR: neutrophil to lymphocyte ratio ; PLR: platelet to lymphocyte ratio; NA: not available.

as a potential trigger of haemodynamic dysfunction in AUPVP patients. Chuang et al. compared 29 VAH (right/left: 23/6) in AUPVP subjects and six VAH in controls (right/left: 5/1). There was a high accordance rate between the side of VAH and AUPVP: 65.5% of the patients had an ipsilateral AUPVP, in which left VAH showed a higher accordance rate (83.3%). VAH accordance showed higher risk (81%) for AUPVP subjects with a vascular risk compared to those without (25%) [19]. The authors suggested that VAH contributes as a risk factor for the development of ipsilateral AUPVP, and is enhanced by atherosclerotic risk factors. Of interest, the accordance rate of VAH and AUPVP was 81% in the vascular risk group compared to 28% in the non-vascular risk group. Comparing VAH presence as a prognostic factor, the same study group showed vestibular paresis to be higher (56.8%) in AUPVP subjects with VAH (n = 29) compared to AUPVP subjects (n = 40) without VAH (37.4%) (p = 0.01). The likely conclusion suggested comorbid VAH might predispose to AUPVP [20]. Moreover, the arterial stiffness has been proposed as a surrogate marker for vascular disease in AUPVP. In a prospective case-control study including 58 AUPVP patients versus 58 controls, arterial stiffness was measured by brachial-ankle pulse wave velocity [21]. Clearly, a higher brachial-ankle pulse wave velocity and higher prevalence of metabolic syndrome was observed in the AUPVP group compared to the control group (p = 0.002 and p = 0.001, respectively, Tab. IV). The authors concluded that these findings support the hypothesis of a vascular aetiology of AUPVP. However, cardiovascular risk factors had limited value in predicting the clinical course of AUPVP.

Studies investigating inflammatory markers in AUPVP

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been considered easily accessible inflammatory markers. Şahin et al. compared 104 AUPVP patients with 138 healthy subjects showing a significant higher NLR and PLR value in the AUPVP group ($p < 0.001$, Tab. IV), supporting the inflammatory role in AUPVP [26]. The same authors have also found an elevated mean platelet volume (MPV) in AUPVP patients proposing this finding as a risk marker for platelet activation, suggesting a vascular cause. Also, Oh et al. studied the inflammatory and thrombotic pathogenesis of acute unilateral vestibulopathy through gene expression profiling combined with bioinformatics analysis in 10 AUPVP patients and 10 controls [24]. They searched differentially expressed genes (DEGs) between these two groups. Interestingly, there were 57 DEGs (50 up-regulated and 7 down-regulated) identified in the patient's group and most of the up-regulated DEGs were significantly related to the neutrophil-mediated immune pathway. They completed the study with comparison of complete blood count tests in 72 patients and in age-matched controls, showing that the NLR was significantly higher in the patients than in the controls (Tab. IV). Thus, they concluded that neutrophil-mediated immune pathway may contribute to the development of AUPVP by mediating inflammatory and thrombotic changes in the vestibular organ.

Studies investigating cardiovascular risk factors in AUPVP

Based on a cross-sectional retrospective study of 160 confirmed VN patients, Oron et al. concluded that cardiovascular pathology and/or cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease and prior cerebral vascular accident/TIA) were significantly associated with AUPVP compared to the general population (Tab. IV) [25]. However, Han et al. did not found significant differences regarding hypertension, diabetes mellitus and dyslipidaemia between AUPVP patients and controls. Nevertheless, the prevalence of carotid plaques was significantly higher in AUPVP patients [22].

In a prospective population-based study, 79 patients with recent AUPVP were followed in 2 different Croatian cities, for 2 years (2011-2012) with the evaluation of the impact of months, seasons and comorbidities [18]. No significant differences between months and seasons were detected. They observed that a significant proportion of AUPVP patients older than 50 years had vascular risk factors, namely, hypertension (30.4%), diabetes mellitus (8.9%), hyperlipidaemia (7.5%) and hypothyreosis (6.3%). Navari studied the results of caloric tests, VHIT and VEMPs in 59 patients with AUPVP [23]. They concluded that there was no effect of age regarding spontaneous recovery and vestibular rehabilitation. Moreover, they observed that most patients exhibited total end-organ damage, which could be related to damage of the entire labyrinth or, more probably, due to a neuritis of the two divisions of the vestibular nerve. Other studies also sought to analyse the vestibular lesion patterns and their connection with the distribution of the neurological afferents.

In the work of Uffer et al., the authors did not evaluate CVRFs, but they tested in what percentage of AUPVP patients the vestibular lesion pattern was observed at odds with the vestibular innervation anatomy [28]. Among the 25 patients, 19 (76%) had a lesion pattern that looked more like an intra-labyrinthine pattern than a neuritis pattern. Half of the patients with a definite intra-labyrinthine pattern had major dysfunction differences in the receptors of the superior vestibular nerve, the other half had dysfunction differences in the receptors of the inferior vestibular nerve. The authors concluded that the results do not support

Table IV. Main results of studies comparing cardiovascular risk factors and inflammation markers.

Outcome	First author	Patients	Controls	*p*
Hypertension (n)	Chung JH [21]	12	8	0.852
	Oron Y [25 *]	42.5%	11.2%	< 0.05
	Han W [22]	39	29	0.592
Diabetes Mellitus (n)	Chung JH [21]	1	1	0.685
	Oron Y [25 *]	15.62%	6.6%	< 0.05
	Han W [22]	5	5	0.749
Dyslipidaemia	Oron Y [25 *]	25%	6.1%	0.05
Cholesterol (± SD)	Chung JH [21] (mg/dL)	181.3 ± 35.0	176.4 ± 37.0	0.575
	Han W [22] (mmol/L)	4.69 ± 0.95	4.73 ± 0.87	0.776
TG (± SD)	Chung JH [21] (mg/dL)	118.2 ± 90.4	146.1 ± 80.7	0.111
	Han W [22] (mmol/L)	1.48 ± 0.96	1.40 ± 1.15	0.661
HDL (± SD)	Chung JH [21] (mg/dL)	49.76 ± 13.8	51.5 ± 13.8	0.507
	Han W [22] (mmol/L)	1.45 ± 0.56	1.47 ± 0.41	0.700
LDL (± SD)	Chung JH [21] (mg/dL)	112.1 ± 32.2	106.4 ± 32.6	0.352
	Han W [22] (mmol/L)	2.57 ± 0.86	2.64 ± 0.73	0.577
MetS Score (± SD)	Chung JH [21]	1.5 ± 1.2	2.2 ± 1.3	0.001
NLR	Şahin Mİ [26] (min-max)	3.23 (0.69-21.21)	1.91 (0.94-4.63)	< 0.001
	Oh EH [24] (± SD)	2.93 ± 2.25	1.54 ± 0.64	< 0.001
PLR	Şahin Mİ [26] (min-max)	145.65 (37.83-696.15)	128.29 (39.63-259.85)	< 0.001
	Oh EH [24] (± SD)	108.21 ± 51.28	125.37 ± 33.98	0.002

*MetS: metabolic syndrome; TG: triglycerides; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SD: Standard Deviation; * Number (n) not available, control group is prevalence among general population.*

the neuritis hypothesis since about three-fourths of patients had an intra-labyrinthine lesion pattern inconsistent with an isolated nerve lesion.

Discussion

The physiopathology of AUPVP needs further exploration concerning the role of viral inflammation and vascular events in the vestibular organ, with significant clinical implications. Acute vertigo may occur due to a labyrinth infarction, but current imaging techniques do not readily allow the identification of isolated labyrinthine infarctions as a cause of acute audiovestibulopathy [13,27]. This systematic review on the vascular mechanisms of AUPVP showed interesting findings. Our first is that comparison of results remains difficult due to the variety of terms used in different studies (Tab. II). Only recently, the literature has made the shift to the term of AUPVP [3].

Furthermore, it is relevant to discuss the clinical signs in patients with an AICA stroke diagnosis showing isolated otovestibular dysfunction (vertigo, hearing loss and/or tinnitus) with normal MRI imaging one to 10 days before the appearance of neurological symptoms [8]. We may speculate that early symptoms might be caused by early smaller emboli deeper in the AICA vascular territory, namely the inner ear microcirculation. Supportive information are histopathology findings showing vascular occlusion in age-related hearing loss patients who are probably more prone to vascular accidents. Moreover, several cases of labyrinthine infarction have been linked to cardioembolism [29-32] and isolated deafness have also been reported during embolisation of a meningioma [33] or cardiopulmonary bypass surgery [34]. Moreover, artery-to-artery embolism is another mechanism of labyrinthine infarction [35]. Each compartment of the labyrinth may be selectively involved when embolism involves a specific branch of the LA causing isolated vertigo or hearing loss. For example, isolated vertigo may occur without hearing loss when the anterior vestibular artery is only involved, and hearing loss may be an isolated finding when the common cochlear artery is selectively affected [27]. Consequently, the clinical assessment of dizziness/vertigo patients, including accompanied neurological symptoms and signs, the presence of vascular risk factors and findings of ocular motor examination to detect stroke is likely to differentiate between central and peripheral aetiologies, but might also give an indication of the eventual origin of

AUPVP aetiology. We should then attempt to detect MRI infarctions in other territories apart from AICA [27].

Regarding NLR, interesting evidence points to a vascular origin of AUPVP. Oh et al. and Şahin et al. found NLR to be significantly higher in the AUPVP patients than in controls [24,26]. These findings suggest a neutrophil-mediated immune pathway in the development of AUPVP by mediating inflammatory and thrombotic changes in the vestibular organ. Indeed, viral infections usually induce an increase in the lymphocyte count and a decrease in the neutrophil counts, leading to lower NLR values [36]. Similar results were found in sudden sensorineural hearing loss (SSNHL) [37,38]. However, regarding MPV studies, Beyan and Beyan doubted this hypothesis with the argument that MPV-related research was hampered by the differences in MPV measurement standardisation leading to variable results [39].

Aging, as a non-modifiable CVRF, showed no effect on spontaneous recovery and on need of vestibular rehabilitation [23]. In contrast, other CVRFs were significantly associated with AUPVP [25].

Another argument for a distinctive pathogenetic mechanism in AUPVP is the comparison to Bell's palsy. Commonly, AUPVP is approached analogous to Bell's palsy, but important differences exist. First of all, corticosteroids have been found to be effective in the treatment of Bell's palsy, while their effect in AUPVP is less established [40]. This might suggest a different mechanism rather than a similarity. Then, benign paroxysmal positional vertigo (BPPV) is more prevalent in patients with a history of AUPVP (20% of patients will develop BPPV in their lifetime [41]) which also supports a pathogenetic model with involvement of an intralabyrinthine lesion rather than a neuritis hypothesis [28].

This review identified important gaps in the literature regarding the exploration of a vascular etiology in AUPVP. No cohort studies with a control group were found, in contrast to SSNHL studies [42-45]. Similarly, no studies were identified in this search regarding the risk of future vascular events (stroke and myocardial infarction) compared to the studies available for SSNHL [46,47]. Research on this topic is of paramount importance as it could help to clarify the possible presence of a higher vascular risk in AUPVP patients, with clinical relevance. The registration of clinical background and cardiovascular risk factors seems a simple and useful step in this matter. Adjunctive testing like VHIT and VEMPs may detect a specific lesion pattern for the 5 components of the vestibular system, which might be favourable for a neuritis hypothesis or for a vascular insult. When a high suspicion of vascular origin is present, cardiovascular assessment seems a reasonable approach.

Limits of the studies and future directions

There is some variation in the definition of AUPVP, which poses a challenge when trying to compare studies from different authors or clinics. Indirect arguments provided in recent literature sustain some evidence for vascular mechanisms. However, we realise that the majority of studies are retrospective in their analysis, with relatively small sample sizes, with limited data regarding the control group. Larger prospective studies of AUPVP patients could lead to a better diagnostic work-up and more precise therapy.

References

1 Neuhauser HK. The epidemiology of dizziness and vertigo. Handb Clin Neurol 2016;137:67-82. https://doi.org/10.1016/B978-0-444-63437-5.00005-4

2 Muelleman T, Shew M, Subbarayan R, et al. Epidemiology of dizzy patient population in a neurotology clinic and predictors of peripheral etiology. Otol Neurotol 2017;38:870-875. https://doi.org/10.1097/MAO.0000000000001429

3 Strupp M, Mandalà M, López-Escámez JA. Peripheral vestibular disorders: an update. Curr Opin Neurol 2019;32:165-173. https://doi.org/10.1097/WCO.0000000000000649

4 Rujescu D, Hartmann AM, Giegling I, et al. Genome-wide association study in vestibular neuritis: involvement of the host factor for HSV-1 replication. Front Neurol 2018;20:591. https://doi.org/10.3389/fneur.2018.00591

5 Jeong SH, Kim HJ, Kim JS. Vestibular neuritis. Semin Neurol 2013;33:185-194. https://doi.org/10.1055/s-0033-1354598

6 Hegemann SCA, Wenzel A. Diagnosis and treatment of vestibular neuritis/neuronitis or peripheral vestibulopathy (PVP)? Open questions and possible answers. Otol Neurotol 2017;38:626-631. https://doi.org/10.1097/MAO.000000000000139

7 Fife TD, Colebatch JG, Kerber KA, et al. Practice guideline: cervical and ocular vestibular evoked myogenic potential testing: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2017;89:2288-2296. https://doi.org/10.1212/WNL.0000000000004690

8 Kim HA, Lee H. Recent advances in understanding audiovestibular loss of a vascular cause. J Stroke 2017;19:61-66. https://doi.org/10.5853/jos.2016.0085

9 Hilton R. Acute renal failure. BMJ 2006;333:786-790. https://doi.org/10.1136/bmj.38975.657639.AE

10 Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep 2017;14:385-392. https://doi.org/10.1007/s11897-017-0351-y

11 Feroze KB, O'Rourke MC. Transient loss of vision. Treasure Island (FL): StatPearls Publishing 2020. https://www.ncbi.nlm.nih.gov/books/NBK430845/

12 Mei X, Atturo F, Wadin K, et al. Human inner ear blood supply revisited: the Uppsala collection of temporal bone-an international resource of education and collaboration. Ups J Med Sci 2018;123:131-142. https://doi.org/10.1080/03009734.2018.1492654

13 Kim JS, Lee H. Inner ear dysfunction due to vertebrobasilar ischemic stroke. Semin Neurol 2009;29:534-540. https://doi.org/10.1055/s-0029-1241037

[14] Goebel JA, O'Mara W, Gianoli G. Anatomic considerations in vestibular neuritis. Otol Neurotol 2001;22:512-518. https://doi.org/10.1097/00129492-200107000-00018

[15] Cruickshanks KJ, Nondahl DM, Dalton DS, et al. Smoking, central adiposity, and poor glycemic control increase risk of hearing impairment. J Am Geriatr Soc 2015;63:918-924. https://doi.org/10.1111/jgs.13401

[16] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1-34. https://doi.org/10.1016/j.jclinepi.2009.06.006

[17] Howick J. Oxford centre for evidence-based medicine: levels of medicine: Oxford centre for evidence-based medicine 2009. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed Dec 2020.

[18] Adamec I, Krbot SM, Handžić J, et al. Incidence, seasonality and comorbidity in vestibular neuritis. Neurol Sci 2015;36:91-95. https://doi.org/10.1007/s10072-014-1912-4

[19] Chuang YM, Chern CM, Liao WH, et al. Comorbid intracranial vertebral artery asymmetry as a risk factor for severe vestibular neuronitis. Otol Neurotol 2011;32:478-482. https://doi.org/10.1097/MAO.0b013e31820e785c

[20] Chuang YM, Chern CM, Liao WH, et al. Contribution of intracranial vertebral artery asymmetry to vestibular neuropathy. J Neurol Neurosurg Psychiatry 2011;82:823-825. https://doi.org/10.1136/jnnp.2009.203323

[21] Chung JH, Lee SH, Park CW, et al. Clinical significance of arterial stiffness and metabolic syndrome scores in vestibular neuritis. Otol Neurotol 2017;38:737-741. https://doi.org/10.1097/MAO.0000000000001352

[22] Han W, Wang D, Wu Y, et al. Correlation between vestibular neuritis and cerebrovascular risk factors. Am J Otolaryngol 2018;39:751-753. https://doi.org/10.1016/j.amjoto.2018.08.006

[23] Navari E, Casani AP. Lesion patterns and possible implications for recovery in acute unilateral vestibulopathy. Otol Neurotol 2020;41:e250-e255. https://doi.org/10.1097/MAO.0000000000002476

[24] Oh EH, Rhee JK, Shin JH, et al. Neutrophil-mediated immune response as a possible mechanism of acute unilateral vestibulopathy. J Vestib Res 2020;30:363-374. https://doi.org/10.3233/VES-200044

[25] Oron Y, Shemesh S, Shushan S, et al. Cardiovascular risk factors among patients with vestibular neuritis. Ann Otol Rhinol Laryngol 2017;12:597-601. https://doi.org/10.1177/0003489417718846

[26] Şahin Mİ, Kökoğlu K, Gülmez E. Mean platelet volume, neutrophil- and platelet to lymphocyte ratios are elevated in vestibular neuritis. J Clin Neurosci 2019;67:134-138. https://doi.org/10.1016/j.jocn.2019.05.062

[27] Liqun Z, Park KH, Kim HJ, et al. Acute unilateral audiovestibulopathy due to embolic labyrinthine infarction. Front Neurol 2018;9:311. https://doi.org/10.3389/fneur.2018.00311

[28] Uffer DS, Hegemann SC. About the pathophysiology of acute unilateral vestibular deficit - vestibular neuritis (VN) or peripheral vestibulopathy (PVP)? J Vestib Res 2016;26:311-317. https://doi.org/10.3233/VES-160581

[29] Lee H, Kim JS, Chung EJ, et al. Infarction in the territory of anterior inferior cerebellar artery: spectrum of audiovestibular loss. Stroke 2009;40:3745-3751. https://doi.org/10.1161/STROKEAHA.109.564682

[30] Amarenco P, Rosengart A, DeWitt LD. Anterior inferior cerebellar artery territory infarcts. Mechanisms and clinical features. Arch Neurol 1993;50:154-161. https://doi.org/10.1001/archneur.1993.00540020032014

[31] Kumral E, Kisabay A, Ataç C. Lesion patterns and etiology of ischemia in the anterior inferior cerebellar artery territory involvement: a clinical - diffusion weighted - MRI study. Eur J Neurol 2006;13:395-401. https://doi.org/10.1111/j.1468-1331.2006.01255.x

[32] Amarenco P, Hauw JJ. Cerebellar infarction in the territory of the anterior and inferior cerebellar artery. A clinicopathological study of 20 cases. Brain 1990;113:139-155. https://doi.org/10.1093/brain/113.1.139

[33] Watanabe Y, Ohi H, Shojaku H, et al. Sudden deafness from vertebrobasilar artery disorder. Am J Otol 1994;15:423-426.

[34] Wright JL, Saunders SH. Sudden deafness following cardio-pulmonary bypass surgery. J Laryngol Otol 1975;89:757-759. https://doi.org/10.1017/s0022215100080956

[35] Raupp SF, Jellema K, Sluzewski M, et al. Sudden unilateral deafness due to a right vertebral artery dissection. Neurology 2004;27;62:1442. https://doi.org/10.1212/01.wnl.0000120757.35082.35

[36] López-González MA, Abrante A, López-Lorente C, et al. Acute-phase inflammatory response in idiopathic sudden deafness: pathogenic implications. Int J Otolaryngol 2012;216592. https://doi.org/10.1155/2012/216592

[37] Koçak HE, Elbistanlı MS, Acıpayam H, et al. Are neutrophil/lymphocyte and platelet/lymphocyte ratios related with formation of sudden hearing loss and its prognosis? Eur Ann Otorhinolaryngol Head Neck Dis 2017;134:383-386. https://doi.org/10.1016/j.anorl.2016.06.005

[38] Seo YJ, Park YA, Bong JP, et al. Predictive value of neutrophil to lymphocyte ratio in first-time and recurrent idiopathic sudden sensorineural hearing loss. Auris Nasus Larynx 2015;42:438-442. https://doi.org/10.1016/j.anl.2015.04.011

[39] Beyan C, Beyan E. Mean platelet volume values may not be elevated in patients with vestibular neuritis. J Clin Neurosci 2019;70:269. https://doi.org/10.1016/j.jocn.2019.08.052

[40] Fishman JM. Corticosteroids effective in idiopathic facial nerve palsy (Bell's palsy) but not necessarily in idiopathic acute vestibular dysfunction (vestibular neuritis). Laryngoscope 2011;121:2494-2495. https://doi.org/10.1002/lary.22327

[41] Halmagyi GM. Diagnosis and management of vertigo. Clin Med (Lond) 2005;5:159-165. https://doi.org/10.7861/clinmedicine.5-2-159

[42] Fasano T, Pertinhez TA, Tribi L, et al. Laboratory assessment of sudden sensorineural hearing loss: a case-control study. Laryngoscope 2017;127:2375-2381. https://doi.org/10.1002/lary.26514

[43] Wang S, Ye Q, Pan Y. Serum non-high-density lipoprotein cholesterol is associated with the risk of sudden sensorineural hearing loss. Medicine (Baltimore) 2020;99:e19175. https://doi.org/10.1097/MD.0000000000019175

[44] Jalali MM, Nasimidoust Azgomi M. Metabolic syndrome components and sudden sensorineural hearing loss: a case-control study. Eur Arch Otorhinolaryngol 2020;277:1023-1029. https://doi.org/10.1007/s00405-020-05808-z

[45] Koo M, Hwang JH. Risk of sudden sensorineural hearing loss in patients with common preexisting sensorineural hearing impairment: a population-based study in Taiwan. PLoS One 2015;27;10:e0121190. https://doi.org/10.1371/journal.pone.0121190

[46] Kim JY, Hong JY, Kim DK. Association of sudden sensorineural hearing loss with risk of cardiocerebrovascular disease: a study using data from the Korea National Health Insurance Service. JAMA Otolaryngol Head Neck Surg 2018;144:129-135. https://doi.org/10.1001/jamaoto.2017.2569

[47] Kim SY, Lim JS, Sim S, et al. Sudden sensorineural hearing loss predicts ischemic stroke: a longitudinal follow-up study. Otol Neurotol 2018;39:964-969. https://doi.org/10.1097/MAO.0000000000001902

Scientific Paper Number 2

Cardiovascular risk and sudden sensorineural hearing loss: a systematic review and meta-analysis

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Cardiovascular Risk and Sudden Sensorineural Hearing Loss: A Systematic Review and Meta-Analysis

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Objectives/Hypothesis: It was previously suggested that patients with idiopathic sudden sensorineural hearing loss (ISSNHL) have a higher risk of cardiovascular disease. The aim of this study is to determine if ISSNHL patients have an increased cardiovascular risk by means of a systematic review and meta-analysis.

Methods: A systematic literature review was performed using PubMed, Embase, Cochrane Libraries and Web of Science. Studies with a clear definition of ISSNHL, investigating an association between traditional vascular risk factors and ISSNHL were included. Adhering to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, two reviewers extracted the data, assessed the risk of bias and performed the analysis of the collected evidence.

Results: Nineteen case–control studies and two cohort studies were included (102,292 patients). Individual studies argued for higher prevalence of hypercholesterolemia, diabetes mellitus (DM) and higher blood pressure (HBP) in ISSNHL patients with a range of odds ratios (ORs) from 1.03 to 19. Pooled analysis of adjusted ORs revealed a significantly increased risk of ISSNHL for patients with hypertriglyceridemia (OR 1.54; 95% confidence interval [CI] 1.18–2.02) and high levels of total cholesterol (TC) (OR 2.09; 95% CI 1.52–2.87 after sensitivity analysis), but not for HBP, DM, or high levels of low- and high-density lipoproteins.

Conclusion: An association between higher vascular risk profile and ISSNHL seems apparent in high levels of triglycerides (TG) and TC, but more studies are needed to confirm this hypothesis due to the high levels of data heterogeneity in the literature.

Key Words: sudden hearing loss, sudden deafness, cardiovascular risk factors, systematic review, meta-analysis.

Level of Evidence: N/A

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INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a decrease in hearing of ≥30 decibels (dB) affecting at least three consecutive frequencies within 72 h or less.[1] The estimated incidence is at least 5–20 per 100,000/year and the spontaneous recovery rate is 32%–65%.[2] Epidemiological surveys suggest an increasing incidence of sudden deafness.[3] Causal identification is found in only 10%–30% of the cases without sufficient evidence.[1,3] Several causes have been proposed, including infectious, autoimmune, vascular, metabolic, hematological and neurological diseases. A recent history of upper airway infection or concomitant findings of viral infection strongly points toward a viral etiology, which is presumably the predominant cause. However, it does not account for all patients and several features are not explained by viral infections: steroid treatment does not necessarily resolve hearing loss and antiviral treatment does not seem to affect disease outcome.[4] The inaccessibility of the inner ear to study ISSNHL pathology makes it difficult to find an identifiable cause without harming hearing or vestibular function.

Atherosclerosis is accompanied by an autoimmune response to low-density lipoprotein *cholesterol* (LDL-c) and other antigens, that cause ischemic heart disease, strokes and peripheral vascular disease, collectively called cardiovascular disease (CVD).[5] Histopathological studies in the elderly with arteriosclerotic changes throughout the auditory system and a large longitudinal study of a middle-aged cohort showed that atherosclerosis was associated with a higher 5-year incidence of hearing impairment, showing that vascular events can affect the inner ear.[6] Accumulating evidence indicates that traditional cardiovascular risk factors (CVRFs) like high blood pressure (HBP), diabetes mellitus (DM) and dyslipidemia may contribute to ISSNHL.[7–11] However, past reviews reported evidence until 2014 and did not report information from some CVRFs (high levels of triglycerides [TG], high-density lipoprotein cholesterol [HDL-c], and metabolic syndrome [MetS])[7] issues that are addressed in the present work. It was also suggested that patients with

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Additional supporting information may be found in the online version of this article.

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ISSNHL had a higher risk of developing future stroke,[12,13] although ISSNHL was not associated with future acute myocardial infarction.[13,14]

Quaranta et al. reported signs of endothelial dysfunction in ISSNHL and Fisch described the blood pressure dysregulation of the stria vascularis (a process related to age and CVRFs) as a consequence of cochlear atherosclerosis, in which the tunica adventitia loses fibroblasts and becomes thicker, which in turn leads to plasmatic viscosity and platelet aggregation.[15–17] As a consequence, vascular pathology is supposed an important etiological factor of ISSNHL.[18,19]

This systematic review and meta-analysis of case–control and cohort studies aimed to determine if ISSNHL patients have an increased cardiovascular risk.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) updated statement and the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) checklist were followed.[20,21] The study protocol has been published in the PROSPERO database (CRD42021274028).

Literature search and eligibility criteria

A systematic literature search was performed using PubMed, Embase, Cochrane Libraries and Web of Science from inception to 17 October 2021. Our hypothesis statement is that adult patients with ISSNHL (P) with or without known medical treatment (I) have a higher prevalence of CVRFs (O) when compared with individuals without ISSNHL (C) in cohort and case-control studies. The literature search was conducted using the search terms "sudden sensorineural hearing loss," "risk factors," "dyslipidemia," "hypertension," "diabetes," and "vascular" and their synonyms combined. They were adapted for fitting the syntax of each database and no language restrictions were applied. The search strategy details are presented in Supporting Information, Appendix S1. All articles about adult patients evaluating a link between ISSNHL and CVRFs were retained. The duplicates were eliminated. Titles and abstracts were independently screened by two reviewers (S.J.and M.A.) and then the full text was evaluated according to predefined inclusion and exclusion criteria (Supporting Information, Appendix S1). Exclusion criteria included: type of publication (abstract, expert's opinion, review, letter or comment), off-topic publications and outcome measure not DM, HBP, Dyslipidemia or Metabolic Syndrome. Apart from the topic, inclusion criteria for the review were: definition of ISSNHL clearly stated, type of the article (prospective/retrospective cohort studies of consecutive patients, case-control studies of consecutive patients) and ISSNHL adult patients (aged >18). The primary outcome was the presence of CVRFs in ISSNHL patients compared to control groups. This electronic search was supplemented by a manual examination of references cited in articles for additional studies. Disagreements regarding study selection were resolved by consensus between authors. Around 21 studies were retained for further analysis.

Data extraction and risk of bias assessment

The following information of the included studies was extracted using a standardized form: author, year of publication, country of publication, number of patients with ISSNHL and controls, evaluated CVRFs, inclusion period, crude and adjusted analysis. The risk of bias in the eligible studies was assessed using the modified Newcastle-Ottawa scale (NOS) as has been applied in previous systematic reviews of case-control and cohort studies.[22] The risk of bias was assessed in three main areas: Selection, Comparability and Exposure (case-control studies)/ Outcome (cohort studies). The modified NOS consist of eight items with 3 subscales, and the total maximum score of these 3 subsets is 9. The thresholds for assessment of the evidence quality were set according to standards of the Agency for Healthcare Research and Quality published by McPheeters et al.[23] As for study eligibility, disagreements regarding risk of bias were resolved by discussion until consensus.

Statistical analysis

Quantitative analysis of the data was performed using descriptive statistics. If no confidence intervals (CIs) were presented, they were calculated from p values. Forest plots with pooled odds ratios (ORs) were produced using Stata version 16 software (StataCorp, College Station, TX). The heterogeneity among the studies was assessed using the I^2 statistic (low 0%–50%, moderate 50%–75%, high >75%). If moderate and high heterogeneity existed, sensitivity analysis was performed limiting the assessment to high-quality studies (in accordance with the risk of bias analysis) to assess if subgroup effects were consistent with the direction of effect of the entire group. To further explore potential sources of heterogeneity, exclusion of outliers was also performed to confirm or not the direction of effect. If high heterogeneity in pooled data was observed, increased caution in interpretation was mandatory. In the case of an I^2 statistic >50%, which indicates the existence of heterogeneity between studies, a random-effects model was utilized; if I^2 statistic is <50%, a fixed-

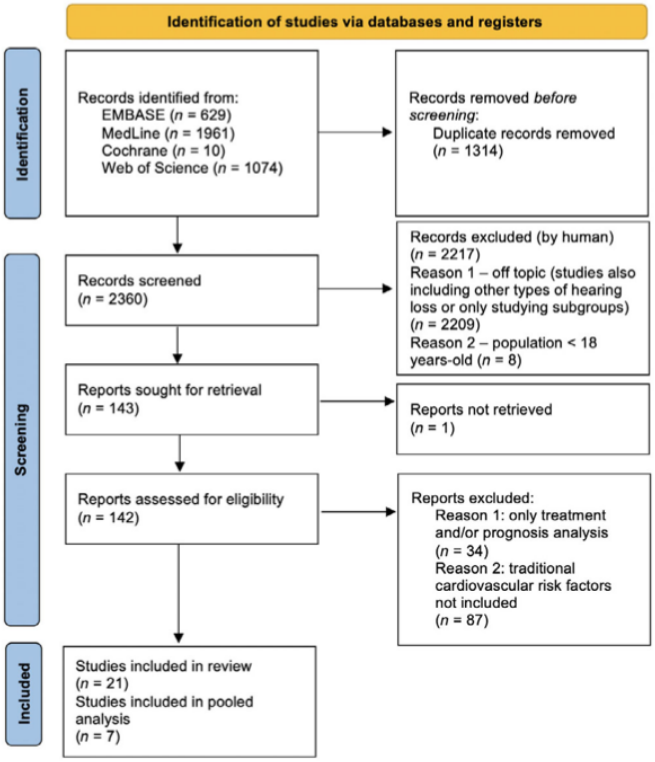

Fig. 1. PRISMA flow diagram of the systematic review (last search date: October 17, 2021). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE I.
Characteristics of the Included Studies on the Association of ISSNHL with Traditional Vascular Risk Factors.

Author, Year	Country	Study Design	Potential Risk Factors	InclusionPeriod	ISSNHL Patients	Controls	Controls Matched for	Statistical Analysis Adjusted for
Aimoni, 2010[24]	Italy	CC Study	DM, Dyslipidemia, HBP	January 2001 to December 2005	141	271	Sex and age	MLR - DM, Smoking, HBP, TC, TG
Cadoni, 2010[25]	Italy	CC Study	Dyslipidemia	Not reported	43	43	Not reported	MLR - Age, sex, Q10, LDL-c, BA, DA, LA, NA, OA
Cadoni, 2007[26]	Italy	CC Study	Dyslipidemia	Not reported	30	60	Not reported	MLR - Age, sex, Q10, LDL-c, TC, homocysteine
Capaccio, 2007[18]	Italy	CC Study	Dyslipidemia	January 2001 to June 2005	100	200	Sex and age	MLR - MTHFR C677T and A1298C, prothrombin G20210A, platelet GlyIIIa, V Leiden G1691A, fibrinogenemia, cholesterolemia, homocystinemia, folatemia
Chang, 2014[27]	Taiwan	Prospective Cohort Study	Dyslipidemia	January 1, 2001 to December 31, 2006	73,957	73,957	Sex, age, DM, HBP	MLR - Hypercholesterolemia, HBP, DM, stroke, sex, age, CKD, CAD, geographic region, income
Chien, 2015[28]	Taiwan	CC Study	MetS	October 2010 to September 2012	181	181	Sex, age	MLR - Age, sex, smoking, DM, HBP, hyperlipidemia
Ciccone, 2012[29]	Italy	CC Study	DM, smoking, Dyslipidemia, HBP	Not reported	29	29	Not reported	MLR - TC, HBP, DM, sex, age, HDL-C, LDL-C, TG, BMI, Fibrinogen
Fasano, 2017[10]	Italy	CC Study	DM, Dyslipidemia	January 2014 to June 2015	131	77	Sex, age	N.A.
Jalali, 2020[30]	Iran	CC Study	MetS and its components	January 2018 to July 2019	81	243	Sex, age	MLR - HBP, TG, HDL-C
Kaneva, 2019[31]	Russia	CC Study	Dyslipidemia	Not reported	27	24	Not reported	MLR - apoB/apoA-I ratio, ATH index
Lee, 2015[32]	Republic of Korea	CC Study	Dyslipidemia	January 2009 to February 2012	324	972	Sex, age, height, HBP, DM, CAD, stroke	MLR - Age, TC, HDL-C, TG, LDL-c, BMI
Lin, 2012[33]	China	Retrospective Cohort Study	DM	2000 to 2004	26,556	26,556	Sex, age, area of residence	MCR - DM, Age, Sex, Stroke, CAD, CKD, retinopathy, geographic region, income
Mohammed, 2014[34]	Iraq	CC Study	Dyslipidemia, glycemia	February 2011 to July 2013	22	55	Sex, age	N.A.
Oreskovic, 2011[35]	Croatia	CC Study	Dyslipidemia	2000 to 2007	54	55	Not reported	N.A.
Rajati, 2016[36]	Iran	CC Study	DM, Dyslipidemia, HBP	September 2011 to September 2012	30	30	Sex, age	MLR - HBP
Rinaldi, 2020[37]	Brazil	CC Study	DM, Dyslipidemia, HBP, MetS	January 2017 to November 2018	39	44	Sex, age	N.A.
Wang, 2019[38]	China and Republic of Korea	CC Study*	Dyslipidemia	2009 to 2012	324	972	Sex, age, height, HBP, DM, CAD, stroke	MLR - sex, age, BMI, DM, CKD, triglyceride, HDL-C and LDL-C, TC, total cholesterol
Wang, 2020[39]	China and Republic of Korea	CC Study*	Dyslipidemia	2009 to 2012	324	972	Sex, age, height, HBP, DM, CAD, stroke	MLR - sex, age, BMI, DM, CKD
Weng, 2013[40]	China	CC Study	Dyslipidemia	January 2007 to December 2012	250	250	Sex, age, weight	MLR - TC, HDL-C, LDL-C, TG, apoA/B, Lp(a)

(Continues)

TABLE I.
Continued

Author, Year	Country	Study Design	Potential Risk Factors	InclusionPeriod	ISSNHL Patients	Controls	Controls Matched for	Statistical Analysis Adjusted for
Marcucci, 2005[41]	Italy	CC Study	DM, Dyslipidemia, HBP	Not reported	155	155	Sex, age	MLR - sex, age, HBP, TC, TG, smoking
Rudack, 2006[42]	Germany	CC Study	DM, HBP	Not reported	142	84	Sex, age	N.A.

AIP = atherogenic index in plasma; apoA = apolipoprotein A; apoB = apolipoprotein B; ATH index = atherogenic index; BA = Behenic acid; BMI = Body mass index; CAD = coronary artery disease; CC = Case-Control; CKD = Chronic Kidney disease; DA = Docosahexaenoic acid; DM = diabetes mellitus; HBP = high blood pressure; HDL-c = high-density lipoprotein cholesterol; ISSNHL = Idiopathic sudden sensorineural hearing loss; LA = Linolenic acid; LDL-c = low-density lipoprotein cholesterol; Lp(a) = lipoprotein a; MCR = multivariate Cox regression; MetS = Metabolic syndrome; MLR = multivariable logistic regression; N.A. = Not available; NA = Nervonic acid; OA = Oleic acid; Q10 = Co-enzyme Q10; TC = total cholesterol; TG = triglycerides.
*Secondary analysis of Lee, 2015.[32]

effects model was used. Results are presented as odds ratios (ORs) with 95% CIs. In case of sufficient number of publications ($n = 10$), publication bias would be assessed via funnel plots. A two-sided p value <0.05 was set to be statistically significant in studies analysis.

RESULTS

Search Strategy and Risk of Bias Assessment

A total of 3,674 records were identified in the initial search. After removing 1,314 duplicates, 2,360 papers remained to screen for potential eligibility. After reading the title and abstracts, 143 studies were retrieved according to the exclusion criteria (Fig. 1). Then, the full article was independently read (SJ and MA) to confirm the eligibility of the article. One article was not retrieved (Supporting Information, Appendix S1) and 121 studies were beyond the scope (34 with only treatment and/or prognosis analysis, 87 without traditional cardiovascular risk factors), resulting in 21 studies (102,292 ISSNHL patients) that met all the inclusion criteria.

Details of the included articles and main conclusions are shown in Table I and Table S1. For pooled analysis, seven studies were included (874 ISSNHL patients), all with a case-control design (Table S2). Eighteen studies assessed the presence of dyslipidemia in ISSNHL[10,18,24–27,29–32,34–41] [HDL-c, low-density lipoprotein cholesterol (LDL-c), total cholesterol (TC), TG and non-HDL-c], nine studies assessed DM,[10,24,29,30,33,34,36,37,41,42] two studies reported MetS[28,30] and seven studies analyzed the HBP between cases and controls (Table I and II and Table S3).[29,30,36–38,41,42] Only four studies specified ISSNHL treatment and different protocols were used, but this analysis was beyond the scope of this study.[25,28,30,37] Results from cohort studies were not pooled because only two publications were retrieved, reporting different outcomes (DM[33] and Hypercholesterolemia[27]). Four studies only presented unadjusted results (Table S4).[30,39,40,42] Regarding CVRFs parameters in the pooled analysis, TC and HDL-c presented with high heterogeneity among the studies (I^2 statistic >75%). In most studies, controls were matched for age and gender, as well as CVRFs such as HBP, DM and dyslipidemia. However, five studies did not present matched controls.[10,34,35,37,42] All studies with adjusted analysis for confounders used either logistic regression model or Cox proportional hazards model. Most studies analyzed hospital-based patients and three studies included administrative datasets from the Taiwan National Health Insurance Research Database.[27,32,33] Two included studies presented a secondary analysis of Lee et al., and were therefore not pooled to avoid the inclusion of identical patients.[38,39] Inclusion periods ranged from 2001 to 2012. Two studies had an overlap of the follow-up period between 2001 and 2004, but the analyzed CVRFs were distinct (Table I).[27,33]

In the cohort studies, the overall quality of the included studies was good (Table S5). In contrast, the quality of the evidence of case-control studies were distributed as follows (Table S6): 47.4% good (9/19 studies), 26.3% fair (5/19 studies), 26.3% poor (5/19 studies).

TABLE II.
Summary of Characteristics of Studies Analyzing Dyslipidemia, HBP and DM

First Author	Cases *N*, Mean Age ± SD, Sex, male/female	Outcome	Measures in cases	Measures in controls	First Author	Cases N, Mean Age ± SD, Sex, male/female	Outcome	Measures in cases	Measures in controls
Fasano, 2017[10]	131, 54 ± 16.2, 71/60	Glucose	98. ± 2.42	82.5 ± 10.1	Cadoni, 2007,[26] 2010[25]	30/43, 45.5 ± 22.5, /50 ± 14, NA/NA;19/24	LDL-C	131 ± 32.4	110.8 ± 22.7
		LDL-c	112.9 ± 2.82	123.2 ± 27.8			TC	213 ± 44	175 ± 21.4
		HDL-c	56.8 ± 1.27	58.4 ± 12.0			LDL-C	128 ± 35.89	110.7 ± 31.34
		TC	187.2 ± 3.30	194.4 ± 28.9			TC	200 ± 38.95	175 ± 26.51
Jalali MM, 2020[30]	81, 45.2 ± 14.6, 44/37	HDL-C	43.0 ± 7.7	46.5 ± 8.0	Kaneva AM, 2019[31]	27, 39.7 ± 12, 27/0	TC,mmol/L	4.26	4.09
		LDL-C	99.0 ± 24.7	103.3 ± 22.0			HDL-C, mmol/L	1.36	1.39
		TG	172.9 ± 97.3	144.8 ± 74.8			LDL-C, mmol/L	2.55	1.92
		TC	176.0 ± 33.0	178.4 ± 26.4			TG,mmol/L	1.23	1.02
		DM, *n* (%)	9 (11.1)	13 (5.3)			ATH index	2.63	1.31
		HBP, *n* (%)	12 (14.8)	7 (7.0)					
Wang, 2020[39]	324, 49.6 ± 16.5, 162/162	TG	122.8 ± 77.2	109.6 ± 65.3	Capaccio, 2007[18]	100, 48.12 ± 14.6, 56/44	TC	224.8 ± 32.6	185.8 ± 18.5
		TC	192.8 ± 33.9	183.5 ± 34.9					
		HDL-C	57.6 ± 15.3	54.3 ± 13.0					
		LDL-C	110.7 ± 35.6	107.2 ± 31.2					
		HBP, *n* (%)	71 (21.91)	175 (18)					
		DM, *n* (%)	41 (12.65)	86 (8.85)					
Mohammed AA, 2014[34]	22, 44.7 ± 11.3, 11/11	TC	190.5 ± 43.2	145.1 ± 31.5	Rinaldi, 2020[37]	39, 48.34 ± 11.13, 23/16	TC	193.69 ± 37.77	188.89 ± 38.44
		HDL-C	48.3±8.75	49.7 ± 8.77			HDL-C	56.08 ± 13.19	54.61 ± 13.33
		LDL-C	118.6 ± 36.0	81.8 ± 34.2			LDL-C	118 ± 33.80	113.87 ± 32.28
		TG	124.5 ± 52.5	73.6 ± 27.7			TG	106 ± 66.6	103.04 ± 69.47
		Glucose	104.7 ± 34.9	84.7 ± 8.36			Glucose	101.30 ± 18.65	87.20 ± 11.85
Oreskovic, 2011[35]	54, 55 ± 14, 31/23	TC,mmol/L	5.9 ± 1.1	5 ± 1.0	Wang, 2019[38]	324, 49.64 ± 16.52, 162/162	TC	215 (194–241)	181 (159–202)
		HDL-C, mmol/L	1.4 ± 0.5	1.4 ± 0.4					
		LDL-C, mmol/L	3.7±0.9	2.9 ± 0.8					
		TG,mmol/L	1.6 ± 0.8	1.6 ± 0.9					
Rajati, 2016[36]	30, 45 ± 12.7, 15/15	TC	207.8 ± 50.8	196.6 ± 46.7	Aimoni, 2010[24]	141, 54.6 ± 15.8, 75/66	TC	227.2 ± 40.0	214.4 ± 40.8
		HDL-C	51.9 ± 9.6	47.5 ± 13.5			TG	124.4 ± 64.9	128.4 ± 101.9
		LDL-C	135.4 ± 37.3	124.6 ± 38.6			DM (%)	15.6	8.5
		TG	124.2 ± 67.8	131.1 ± 67.3	Weng, 2013[40]	250, 56.41 (15–84), 137/113	TC,mmol/L	4.74 ± 1.02	4.38 ± 0.94
		Glucose	105.3 ± 33.5	100.7 ± 39			HDL-C, mmol/L	1.43 ± 0.40	1.46 ± 3.25
		HBP (%)	7.16	40			LDL-C, mmol/L	2.68 ± 0.86	2.38 ± 0.73

(Continues)

TABLE II.
Continued

First Author	Cases *N*, Mean Age ± SD, Sex, male/female	Outcome	Measures in cases	Measures in controls	First Author	Cases N, Mean Age ± SD, Sex, male/female	Outcome	Measures in cases	Measures in controls
Marcucci, 2005[41]	155, 54 (19–79), 67/88	TG, *n* (%)	31 (20)	8 (5.1)			TG,mmol/L	1.32 ± 0.97	4.38 ± 0.94
		TC, *n* (%)	52 (33.5)	11 (7.0)	Rudack, 2006[42]	142, 51.2 ± 17.2, 77/65	HBP, *n* (%)	20 (14.1)	20 (23.8)
		HBP, *n* (%)	25 (16.1)	18 (11.6)			DM, *n* (%)	8 (5.6)	2 (2.4)
Ciccone, 2012[29]	29, 54 ± 15, 19/10	TC	188 ± 33	171 ± 29	Lee JS, 2015[32]	324, 49.64 ± 16.52, 162/162	TC	192.82 ± 37.9	183.46 ± 34.89
		HDL-C	48 ± 10	49 ± 13			HDL-C	57.62 ± 15.3	54.34 ± 13.05
		LDL-C	118 ± 27	101 ± 28			LDL-C	110.65 ± 35.61	107.21 ± 31.25
		TG	109 ± 45	105 ± 51			TG	122.78 ± 77.21	109.63 ± 65.32
		HBP, *n* (%)	17 (58)	12 (41)					

Glucose, LDL-c, HDL-c, TC and TG in mg/dl (except if other unit is indicated) ± SD.
ATH index = atherogenic index; BMI = Body mass index; DM = diabetes mellitus; HBP = high blood pressure; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; MetS = Metabolic syndrome; NA = Not available; SBP = Systolic blood pressure; SD = Standard Deviation; TC = total cholesterol; TG = triglycerides.

Risk of ISSNHL in the presence of CVRFs

Dyslipidemia. The results from the 18 studies that analyzed this risk factor in ISSNHL patients are heterogeneous (Table II). From TG pooled analysis, a total of 701 ISSNHL patients and 1,641 controls were included with an overall OR of 1.54; 95% CI 1.18–2.02 (Fig. 2a). The overall OR for TC considering 720 patients and 1,598 controls was 2.82; 95% CI 0.88–9.04 (Fig. 2b). Because, high heterogeneity was observed ($I^2 = 97\%$), a sensitivity analysis was executed excluding the study with highest risk of bias[18] and the outlier.[41] This analysis showed a significant overall OR of 2.09; 95% CI 1.52–2.87, $I^2 = 0\%$ (Fig. 2c). When pooling the LDL-c adjusted ORs ranging from 0.17 to 0.81 and including 397 ISSNHL patients, a non-significant overall OR of 0.78 (95% CI 0.52–1.18) was found (Fig. 3a). If the study of Lee et al.[32] was eliminated from the analysis due to its skewed weight (96.23%), the trend to a non-significant OR would have persisted [0.29 (95% CI 0.03–2.40)]. High heterogeneity and a non-significant overall OR were obtained from HDL-c analysis (Fig. 3b).

Diabetes mellitus. For DM, some studies showed a higher prevalence in patients with ISSNHL,[24,34,37,38] but others[30,36] found no significant difference between cases and controls. Pooling of adjusted ORs was not possible because only one study would be included.[24] However, when pooling unadjusted OR values, an overall non-significant result was found (OR 1.33 (95% CI 0.58–3.09, Fig. 4a).

High blood pressure. Seven studies evaluated the presence of HBP in ISSNHL patients compared with controls, but results are inconclusive (Table II).[29,30,36–38,41,42] Overall analysis of adjusted ORs showed a non-significant result (OR 1.04; 95% CI 0.42–2.56, Fig. 4b).

Metabolic syndrome. Chien et al. showed that MetS components were independent risk factors for ISSNHL.[28] The three components (waist circumference, HBP and DM) were all significantly higher in ISSNHL patients than in the control group (Table S3). Jalali MM & Azgomi MN showed a trend of the odds for ISSNHL with the increasing number of MetS components, ranging from an OR of 2.70 (95% CI 1.19–6.12) for one component, to an OR of 16.22 (95% CI 2.18–120.76) for four components.[30] A pooled analysis was not performed because one study presented adjusted results[28] and the other unadjusted results.[2]

DISCUSSION

The present systematic review included 21 studies (102,292 ISSNHL patients) and a quantitative analysis was conducted on seven studies to assess the link between CVRFs and the ISSNHL. Our results showed that hypertriglyceridemia may be an independent risk factor for ISSNHL, increasing the risk 1.54-fold. After sensitivity analysis, hypercholesterolemia was also presented as a potential independent risk factor for ISSNHL.

Sudden sensorineural hearing loss is a diagnostic challenge as various mechanisms were proposed but

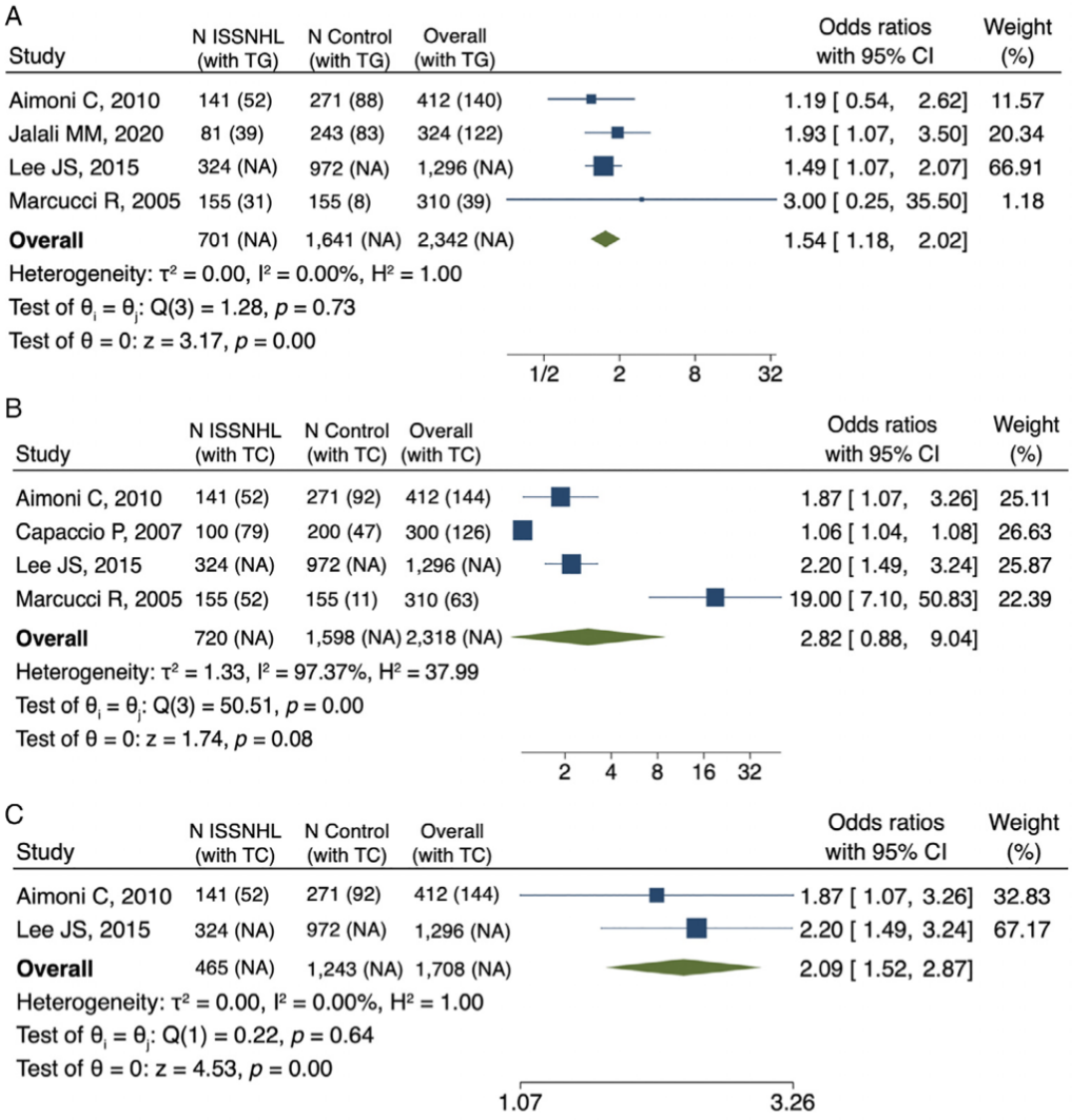

Fig. 2. Forest Plot odds ratios for the risk of ISSNHL in groups with hypertriglyceridemia (A) and high levels of total cholesterol (B - without sensitivity analysis; C - with sensitivity analysis). NA = not available; TC = high levels of total cholesterol; TG = hypertriglyceridemia. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

frequently no underlying disease can be found. Recently, the association between migraine and ISSNHL was analyzed in one meta-analysis. Migraine was associated with a 1.8-fold increased risk of developing ISSNHL, exploring the possibility of a vascular etiology in ISSNHL.[43] On the other hand, recent works indicated that ISSNHL may be an independent risk factor for the development of stroke, especially in elderly patients.[13] Vascular mechanisms in acute unilateral peripheral vestibulopathy were also proposed.[44] Acute vertigo may occur due to a labyrinth infarction, but current imaging techniques do not readily allow the identification of isolated labyrinthine infarctions as a cause of acute audiovestibulopathy.[45,46]

Cochlear microvascular disorders relate to plasma viscosity and thrombotic events. The proposed mechanism is lipotoxicity of blood vessels inducing atherosclerotic changes with endothelial injury, resulting in cochlear microangiopathy with decreased blood supply.[10] Ullrich et al.[47] and Ballesteros et al.[48] found an identical frequency of CVRFs between controls and ISSNHL patients. Conversely, as seen in this work, many studies showed conflicting results (Table II). The weakness of these studies remains in their retrospective analysis, relatively small population sizes, univariate analysis, lack of longitudinal data and no standardized verification of the diagnosis with audiometric data. In addition, studies evaluating lipids levels did not use the same threshold concentrations to define pathology (Table S2).

A systematic review and meta-analysis of the risk factors for ISSNHL from 2012 concluded that smoking (OR of 1.34; 95% CI 1.12–1.61) and heavy alcohol consumption (OR of 2.21; 95% CI 1.68–2.91) appeared to be associated with a higher risk of developing ISSNHL, but no significant association was found for HBP and DM.[8] Nonetheless, the cohort study of Lin et al. found a higher risk of ISSNHL in DM patients (OR 1.59; 95% CI

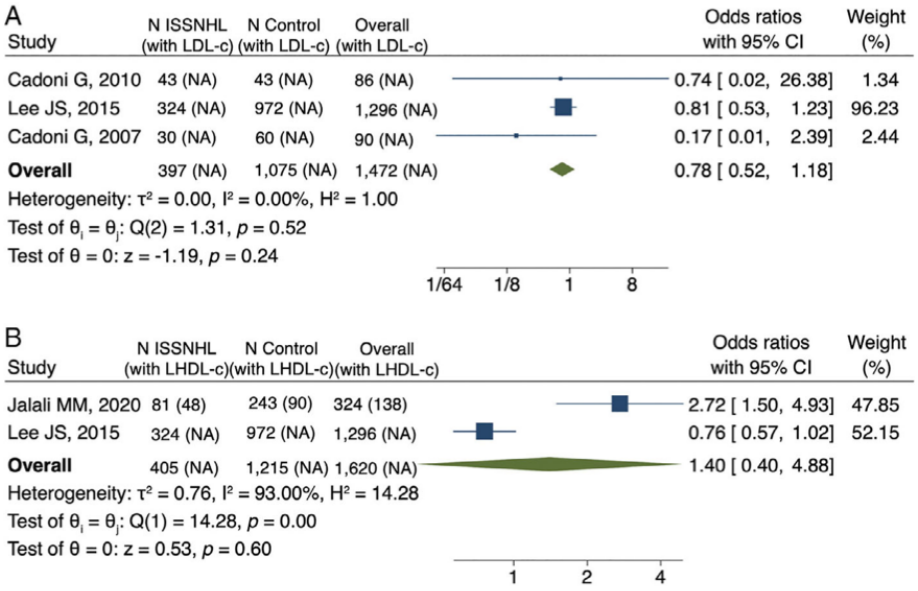

Fig. 3. Forest Plot odds ratios for the risk of ISSNHL in groups with high levels of low-density lipoproteins (A) and low levels of high-density lipoproteins (B). NA = not available; LDL-c = low-density lipoproteins; LHDL-c = low levels of high-density lipoproteins. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

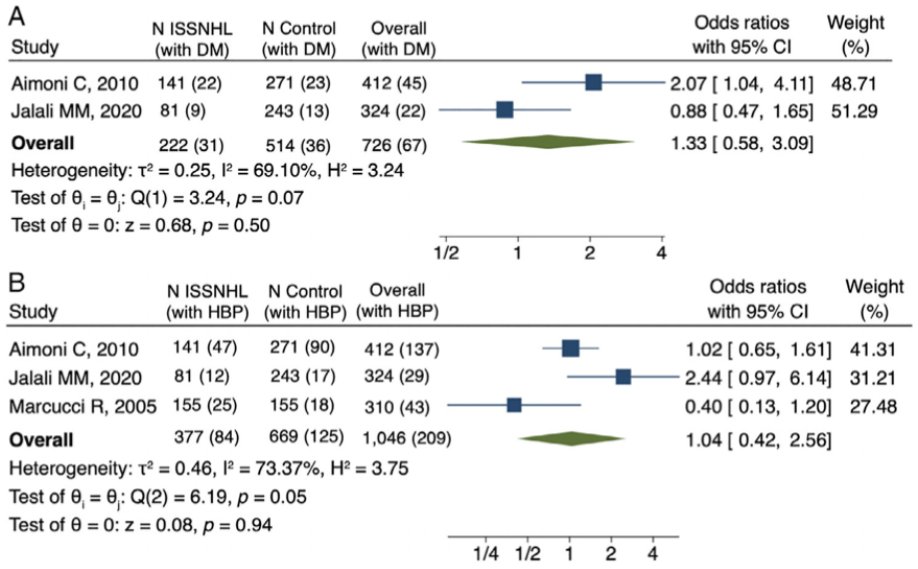

Fig. 4. Forest Plot odds ratios for the risk of ISSNHL in groups with diabetes mellitus (A) and high blood pressure (B). DM = diabetes mellitus; HBP = high blood pressure [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

1.29–1.96).[33] After 3 years, the work of Chang et al. pooled six case-control studies to assess the relationship between serum lipids and ISSNHL.[49] A pooled result was only possible for TC and LDL-c without significant findings. In our work, collected evidence from inception to 2021 has already allowed overall results for more CVRFs such as TG and precise results for TC in sensitivity analysis are available. These results were not described in a meta-analysis until now to the best of our knowledge. Other parameters have been implied in the development of ISSNHL as MTHFR enzyme polymorphisms,[8,9,17] factor V Leiden and factor VIII mutations,[9,10,17] neutrophil/lymphocyte ratio and platelets lymphocyte ratio.[50,51] However, results are not consistent.[8–10,17]

Limitations

The results of this work are limited due to the retrospective nature of the included studies. The high variability in quality and size of the included studies can also induce bias. Another important point is that the best available evidence is from large-scale population

administrative databases, which can be susceptible to administrative inconsistencies. Finally, the heterogeneity of pooled studies was distributed between 0% and 97%, announcing an important variability in studies. This should be considered before incorporating our results into clinical practice.

CONCLUSION

To clarify the relation between CVRFs and ISSNHL, long-term, multi-center and prospective studies are crucial, but difficult to perform, because ISSNHL is not a common clinical entity. At present, medical imaging cannot prove ischemic events in the inner ear, but if this barrier is exceeded, further evidence can be added. Our results showed that hypertriglyceridemia and hypercholesterolemia may be independent risk factors for ISSNHL, increasing the risk 1.54-fold and 2.09-fold, respectively. A diagnostic standardization in patients with ISSNHL is needed regarding cardiovascular comorbidities. The risk factors may be well investigated to develop more evidence on etiologic incidents. Regarding the vascular origin of ISSNHL, we can conclude that there is contradictory evidence on this etiology, that ISSNHL probably is a predominantly multifactorial disease, but a specific group of high vascular risk patients may be more susceptible. If future studies show that ISSNHL may reveal unknown vascular risks, this will have important implications for therapeutic and preventive strategies.

REFERENCES

1. Chandrasekhar SS, Tsai Do BS, Schwartz SR, et al. Clinical practice guideline: sudden hearing loss (update). *Otolaryngol Head Neck Surg*. 2019; 161(1_suppl):S1-S45.
2. Gündogan F, Bayram A, Kalkan M, Özcan Đ. Plasma levels of endothelial cell-specific molecule-1 and pentraxin-3 in idiopathic sudden sensorineural hearing loss. *J Laryngol Otol*. 2018;132:1-5.
3. Chen X, Fu YY, Zhang TY. Role of viral infection in sudden hearing loss. *J Int Med Res*. 2019;47(7):2865-2872.
4. Kim C, Sohn JH, Jang MU, et al. Ischemia as a potential etiologic factor in idiopathic unilateral sudden sensorineural hearing loss: analysis of posterior circulation arteries. *Hear Res*. 2016;331:144-151.
5. Kobiyama K, Ley K. Atherosclerosis. *Circ Res*. 2018;123(10):1118-1120.
6. Fischer ME, Schubert CR, Nondahl DM, et al. Subclinical atherosclerosis and increased risk of hearing impairment. *Atherosclerosis*. 2015;238(2): 344-349.
7. Balakumar P, Maung UK, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacol Res*. 2016;113: 600-609.
8. Lin RJ, Krall R, Westerberg BD, Chadha NK, Chau JK. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. *Laryngoscope*. 2012;122:624-635.
9. Passamonti SM, Di Berardino F, Bucciarelli P, et al. Risk factors for idiopathic sudden sensorineural hearing loss and their association with clinical outcome. *Thromb Res*. 2015;135:508-512.
10. Fasano T, Pertinhez TA, Tribi L, et al. Laboratory assessment of sudden sensorineural hearing loss: a case–control study. *Laryngoscope*. 2017;127: 2375-2381.
11. Fusconi M, Chistolini A, de Virgilio A, et al. Sudden sensorineural hearing loss: a vascular cause? Analysis of prothrombotic risk factors in head and neck. *Int J Audiol*. 2012;51:800-805.
12. Lin HC, Chao PZ, Lee HC. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. *Stroke*. 2008;39(10):2744-2748.
13. Lammers MJW, Young E, Westerberg BD, Lea J. Risk of stroke and myocardial infarction after sudden sensorineural hearing loss: a meta-analysis. *Laryngoscope*. 2021;131(6):1369-1377.
14. Crowson MG, Mulder H, Cyr DD, et al. Idiopathic sudden sensorineural hearing loss is not a sentinel event for acute myocardial infarction. *Otol Neurotol*. 2018;39(7):e518-e523.
15. Quaranta N, De Ceglie V, D'Elia A. Endothelial dysfunction in idiopathic sudden sensorineural hearing loss: a review. *Audiol Res*. 2016;6(1):151.
16. Fisch U, Dobozi M, Greig D. Degenerative changes of the arterial vessels of the internal auditory meatus during the process of aging. A histological study. *Acta Otolaryngol*. 1972;73(2):259-266.
17. Fusconi M, Attanasio G, Capitani F, et al. Is there a relation between sudden sensorineural hearing loss and white matter lesions? *Eur Arch Otorhinolaryngol*. 2019;276(11):3043-3049. Erratum in: *Eur Arch Otorhinolaryngol*. 2019 Sep 10.
18. Capaccio P, Ottaviani F, Cuccarini V, et al. Genetic and acquired prothrombotic risk factors and sudden hearing loss. *Laryngoscope*. 2007; 117(3):547-551.
19. Ohlemiller KK, Gagnon PM. Cellular correlates of progressive hearing loss in 129S6/SvEv mice. *J Comp Neurol*. 2004;469(3):377-390.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
21. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.
22. Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta- analyses. Ottawa, Canada: The Ottawa Health Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 29 September 2021.
23. McPheeters ML, Kripalani S, Peterson NB, et al. Closing the Quality Gap: revisiting the State of the Science (Vol. 3: Quality Improvement Interventions To Address Health Disparities). Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Aug. (Evidence Reports/Technology Assessments, No. 208.3.) Appendix G, Thresholds for Quality Assessment.
24. Aimoni C, Bianchini C, Borin M, et al. Diabetes, cardiovascular risk factors and idiopathic sudden sensorineural hearing loss: a case-control study. *Audiol Neurootol*. 2010;15(2):111-115.
25. Cadoni G, Scorpecci A, Cianfrone F, Giannantonio S, Paludetti G, Lippa S. Serum fatty acids and cardiovascular risk factors in sudden sensorineural hearing loss: a case-control study. *Ann Otol Rhinol Laryngol*. 2010;119(2): 82-88.
26. Cadoni G, Scipione S, Agostino S, et al. Coenzyme Q 10 and cardiovascular risk factors in idiopathic sudden sensorineural hearing loss patients. *Otol Neurotol*. 2007;28(7):878-883.
27. Chang SL, Hsieh CC, Tseng KS, Weng SF, Lin YS. Hypercholesterolemia is correlated with an increased risk of idiopathic sudden sensorineural hearing loss: a historical prospective cohort study. *Ear Hear*. 2014;35(2):256-261.
28. Chien CY, Tai SY, Wang LF, et al. Metabolic syndrome increases the risk of sudden sensorineural hearing loss in Taiwan: a case-control study. *Otolaryngol Head Neck Surg*. 2015;153(1):105-111.
29. Ciccone MM, Cortese F, Pinto M, et al. Endothelial function and cardiovascular risk in patients with idiopathic sudden sensorineural hearing loss. *Atherosclerosis*. 2012;225(2):511-516.
30. Jalali MM, Nasimidoust AM. Metabolic syndrome components and sudden sensorineural hearing loss: a case-control study. *Eur Arch Otorhinolaryngol*. 2020;277(4):1023-1029.
31. Kaneva AM, Yanov YK, Bojko SG, et al. The atherogenic index (ATH index) as a potential predictive marker of idiopathic sudden sensorineural hearing loss: a case control study. *Lipids Health Dis*. 2019;18(1):64.
32. Lee JS, Kim DH, Lee HJ, et al. Lipid profiles and obesity as potential risk factors of sudden sensorineural hearing loss. *PLoS One*. 2015;10(4): e0122496.
33. Lin SW, Lin YS, Weng SF, Chou CW. Risk of developing sudden sensorineural hearing loss in diabetic patients: a population-based cohort study. *Otol Neurotol*. 2012;33(9):1482-1488.
34. Mohammed AA. Lipid profile among patients with sudden sensorineural hearing loss. *Indian J Otolaryngol Head Neck Surg*. 2014;66(4):425-428.
35. Oreskovic Z, Shejbal D, Bicanic G, Kekic B. Influence of lipoproteins and fibrinogen on pathogenesis of sudden sensorineural hearing loss. *J Laryngol Otol*. 2011;125(3):258-261.
36. Rajati M, Azarpajooh MR, Mouhebati M, et al. Is sudden hearing loss associated with atherosclerosis? *Iran J Otorhinolaryngol*. 2016;28(86):189-195.
37. Rinaldi M, Cavallaro G, Cariello M, Scialpi N, Quaranta N. Metabolic syndrome and idiopathic sudden sensori-neural hearing loss. *PLoS One*. 2020;15(8):e0238351.
38. Wang S, Ye Q, Pan Y. Threshold effects between plasma total cholesterol level and the risk of sudden sensorineural hearing loss. *Int J Clin Exp Med*. 2019;12(10):12441-12447.
39. Wang S, Ye Q, Pan Y. Serum non-high-density lipoprotein cholesterol is associated with the risk of sudden sensorineural hearing loss. *Medicine (Baltimore)*. 2020;99(7):e19175.
40. Weng T, Devine EE, Xu H, Yan Z, Dong P. A clinical study of serum lipid disturbance in Chinese patients with sudden deafness. *Lipids Health Dis*. 2013;12:95.
41. Marcucci R, Alessandrello Liotta A, Cellai AP, et al. Cardiovascular and thrombophilic risk factors for idiopathic sudden sensorineural hearing loss. *J Thromb Haemost*. 2005;3(5):929-934.
42. Rudack C, Langer C, Stoll W, Rust S, Walter M. Vascular risk factors in sudden hearing loss. *Thromb Haemost*. 2006;95(3):454-461.
43. Mohammadi M, Taziki Balajelini MH, Rajabi A. Migraine and risk of sudden sensorineural hearing loss: a systematic review and meta-analysis. *Laryngoscope Investig Otolaryngol*. 2020;5(6):1089-1095.
44. Simões J, Vlaminck S, Seiça R, Acke F, Miguéis A. Vascular mechanisms in acute uni- lateral peripheral vestibulopathy: a systematic re- view. *Acta Otorhinolaryngol Ital*. 2021;41:401-409.

45. Kim JS, Lee H. Inner ear dysfunction due to vertebrobasilar is- chemic stroke. *Semin Neurol*. 2009;29:534-540.
46. Liqun Z, Park KH, Kim HJ, Lee SU, Choi JY, Kim JS. Acute unilateral audiovestibulopa- thy due to embolic labyrinthine infarction. *Front Neurol*. 2018; 9:311.
47. Ullrich D, Aurbach G, Drobik C. A prospective study of hyperlipidemia as a pathogenic factor in sudden hearing loss. *Eur Arch Otorhinolaryngol*. 1992;249:273-276.
48. Ballesteros F, Alobid I, Tassies D, et al. Is there an overlap between sudden neurosensorial hearing loss and cardiovascular risk factors? *Audiol Neurootol*. 2009;14(3):139-145. Epub 2008 Nov 13.
49. Chang IJ, Kang CJ, Yueh CY, Fang KH, Yeh RM, Tsai YT. The relationship between serum lipids and sudden sensorineural hearing loss: a systematic review and meta-analysis. *PLoS One*. 2015;10(4):e0121025.
50. Koçak HE, Elbistanl MS, Acıpayam H, Alakras WME, Kıral MN, Kayhan FT. Are neutrophil/lymphocyte and platelet/lymphocyte ratios related with formation of sudden hearing loss and its prognosis? *Eur Ann Otorhinolaryngol Head Neck Dis*. 2017;134(6):383-386.
51. Seo YJ, Park YA, Bong JP, Park DJ, Park SY. Predictive value of neutrophil to lymphocyte ratio in first-time and recurrent idiopathic sudden sensorineural hearing loss. *Auris Nasus Larynx*. 2015;42(6): 438-442.

Scientific Paper Number 3

Cardiovascular risk factors among patients with acute unilateral inner ear hypofunction: a case-control study

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ORIGINAL RESEARCH

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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.

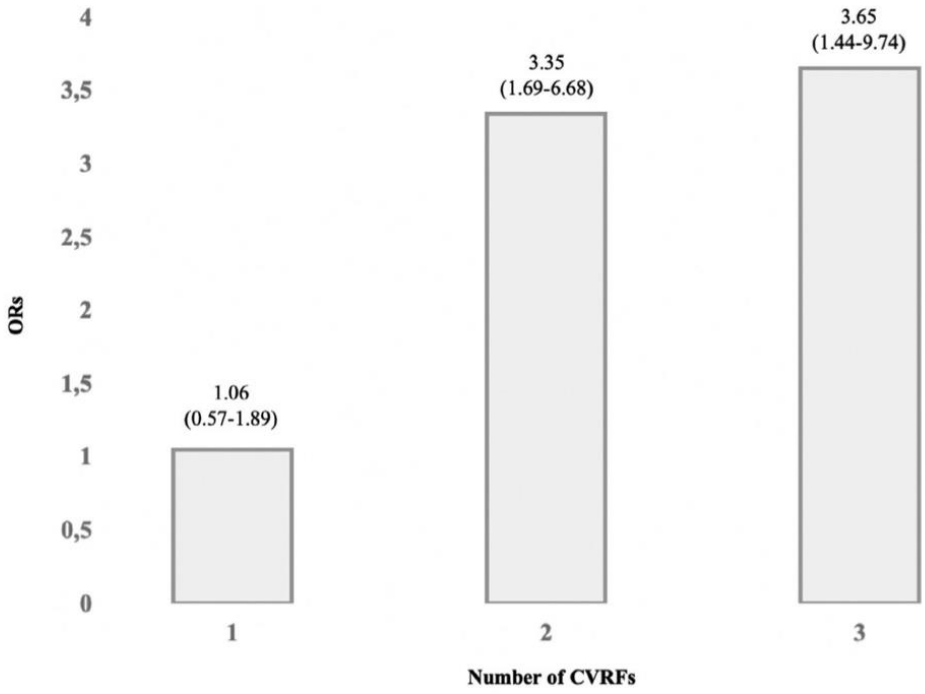
2.4 | Statistical analysis

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.



CVRFs Cardiovascular risk factors; *OR* odds ratio

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

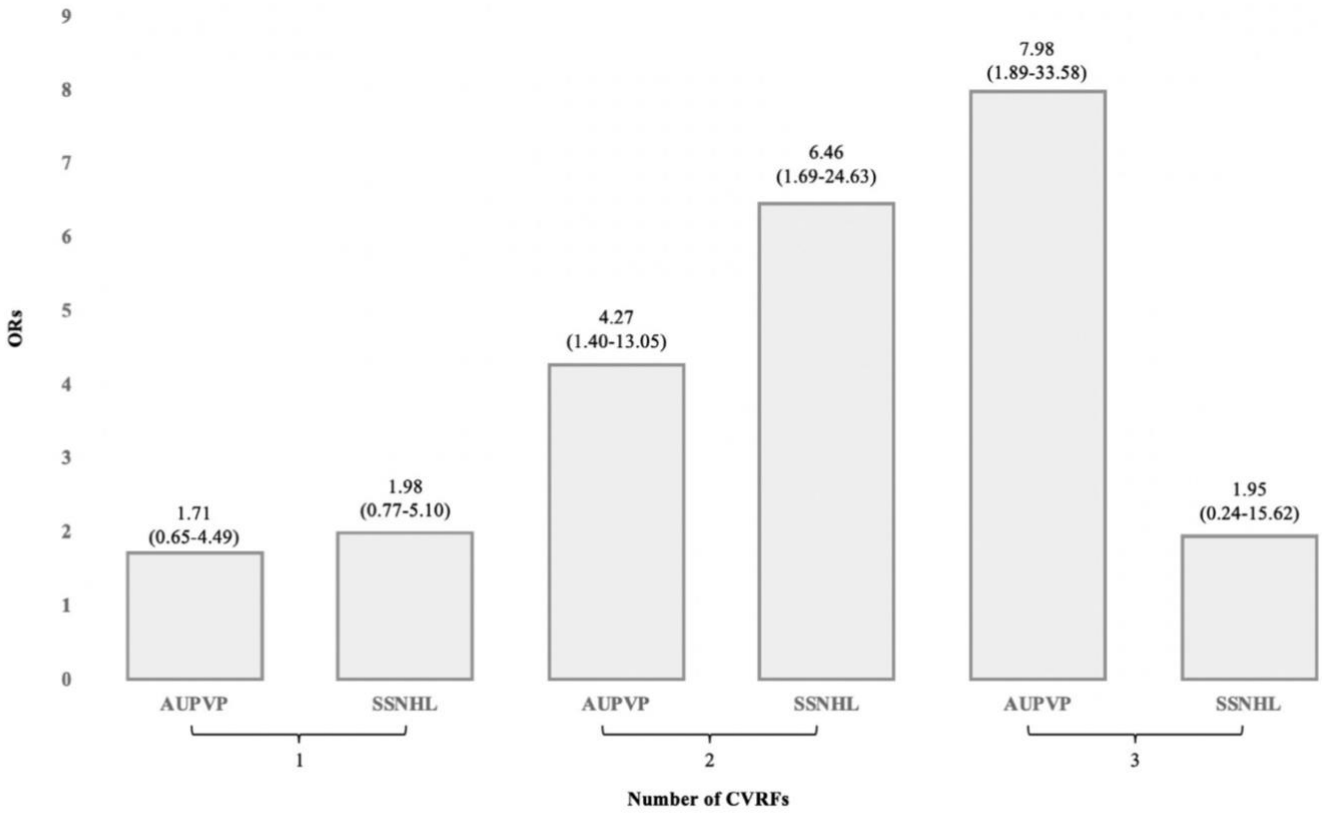
Abbreviations: AUIEH, acute unilateral inner ear hypofunction; CI, confidence interval; CVRF, cardiovascular risk factor; OR, odds ratio.

± 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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REFERENCES

1. Strupp M, Mandalà M, López-Escámez JA. Peripheral vestibular disorders: an update. *Curr Opin Neurol*. 2019;32:165-173.
2. Simões J, Vlaminck S, Seiça R, Acke F, Miguéis A. Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review. *Acta Otorhinolaryngol Ital*. 2021;41:401-409.
3. Jeong SH, Kim HJ, Kim JS. Vestibular neuritis. *Semin Neurol*. 2013;33:185-194.
4. Kim HA, Lee H. Recent advances in understanding audiovestibular loss of a vascular cause. *J Stroke*. 2017;9:61-66.
5. Chandrasekhar SS, Tsai Do BS, Schwartz SR, et al. Clinical practice guideline: sudden hearing loss (update). *Otolaryngol Head Neck Surg*. 2019;161:S1-S45.
6. Chen X, Fu YY, Zhang TY. Role of viral infection in sudden hearing loss. *J Int Med Res*. 2019;47:2865-2872.
7. Gündoan F, Bayram A, Kalkan M, Özcan Đ. Plasma levels of endothelial cell-specific molecule-1 and pentraxin-3 in idiopathic sudden sensorineural hearing loss. *J Laryngol Otol*. 2018;132(11):995-999.
8. Kim C, Sohn JH, Jang MU, et al. Ischemia as a potential etiologic factor in idiopathic unilateral sudden sensorineural hearing loss: analysis of posterior circulation arteries. *Hear Res*. 2016;331:144-151.
9. Mei X, Atturo F, Wadin K, et al. Human inner ear blood supply revisited: the Uppsala collection of temporal bone—an international resource of education and collaboration. *Ups J Med Sci*. 2018;123(3):131-142.

10. Kim JS, Lee H. Inner ear dysfunction due to vertebrobasilar ischemic stroke. *Semin Neurol*. 2009;29(5):534-540.
11. Cruickshanks KJ, Nondahl DM, Dalton DS, et al. Smoking, central adiposity, and poor glycemic control increase risk of hearing impairment. *J Am Geriatr Soc*. 2015;63(5):918-924.
12. Kuo CL, Shiao AS, Wang SJ, Chang WP, Lin YY. Risk of sudden sensorineural hearing loss in stroke patients: a 5-year nationwide investigation of 44,460 patients. *Medicine (Baltimore)*. 2016;95(36):e4841.
13. Crowson MG, Mulder H, Cyr DD, et al. Idiopathic sudden sensorineural hearing loss is not a sentinel event for acute myocardial infarction. *Otol Neurotol*. 2018;39(7):e518-e523.
14. Simões J, Vlaminck S, Seiça R, Acke F, Miguéis A. Cardiovascular risk and sudden sensorineural hearing loss: a systematic review and meta-analysis. *Laryngoscope*. 2022. doi:10.1002/lary.30141
15. Lammers MJW, Young E, Westerberg BD, Lea J. Risk of stroke and myocardial infarction after sudden sensorineural hearing loss: a meta-analysis. *Laryngoscope*. 2021;131(6):1369-1377.
16. Lin RJ, Krall R, Westerberg BD, Chadha NK, Chau JK. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. *Laryngoscope*. 2012;22(3):624-635.
17. Marcucci R, Alessandrello Liotta A, Cellai AP, et al. Cardiovascular and thrombophilic risk factors for idiopathic sudden sensorineural hearing loss. *J Thromb Haemost*. 2005;3(5):929-934.
18. Malay S, Chung KC. The choice of controls for providing validity and evidence in clinical research. *Plast Reconstr Surg*. 2012;130(4):959-965.
19. Li L, Zhang M, Holman D. Population versus hospital controls for case–control studies on cancers in Chinese hospitals. *BMC Med Res Methodol*. 2011;11:167.
20. Lin HC, Chao PZ, Lee HC. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. *Stroke*. 2008;39(10):2744-2748.
21. Oron Y, Shemesh S, Shushan S, et al. Cardiovascular risk factors among patients with vestibular neuritis. *Ann Otol Rhinol Laryngol*. 2017;12:597-601.
22. Jalali MM, Nasimidoust AM. Metabolic syndrome components and sudden sensorineural hearing loss: a case-control study. *Eur Arch Otorhinolaryngol*. 2020;277:1023-1029.
23. Han W, Wang D, Wu Y, Fan Z, Guo X, Guan Q. Correlation between vestibular neuritis and cerebrovascular risk factors. *Am J Otolaryngol*. 2018;39:751-753.
24. Chang SL, Hsieh CC, Tseng KS, Weng SF, Lin YS. Hypercholesterolemia is correlated with an increased risk of idiopathic sudden sensorineural hearing loss: a historical prospective cohort study. *Ear Hear*. 2014;35(2):256-261.
25. Lin SW, Lin YS, Weng SF, Chou CW. Risk of developing sudden sensorineural hearing loss in diabetic patients: a population-based cohort study. *Otol Neurotol*. 2012;33(9):1482-1488.
26. Lee WH, Kim JW, Lim JS, Kong IG, Choi HG. Chronic rhinosinusitis increases the risk of hemorrhagic and ischemic stroke: a longitudinal follow-up study using a national sample cohort. *PLoS One*. 2018;13(3):e0193886.
27. Wang PC, Lin HC, Kang JH. Chronic rhinosinusitis confers an increased risk of acute myocardial infarction. *Am J Rhinol Allergy*. 2013;27(6):e178-e182.
28. Share of the population who has high blood pressure in Belgium in 2018, by age. Accessed August 6, 2022. https://www.statista.com/statistics/1135519/high-blood-pressure-prevalence-population-by-age-belgium/
29. Ligue Cardiologique Belge. Accessed August 6, 2022. https://liguecardioliga.be/cholesterol/
30. Vers une Belgique en bonne santé, État de Santé, Maladies non transmissibles, Diabète. Accessed August 6, 2022. https://www.belgiqueenbonnesante.be/fr/etat-de-sante/maladies-non-transmissibles/diabete

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Scientific Paper Number 4

Audiometric patterns and vascular risk in age-related hearing loss

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For future submission to a journal in the field of Otorhinolaryngology

AUDIOMETRIC PATTERNS AND VASCULAR RISK IN AGE-RELATED HEARING LOSS

ABSTRACT

Objective: To assess whether low-frequency audiometric patterns can predict the presence of vascular risk in a group of age-related hearing loss (ARHL) patients.

Study Design: Retrospective case review.

Setting: ENT practice in hospital setting.

Patients: One hundred fifty-six patients were diagnosed with ARHL between July 2021 and July 2022.

Interventions: Audiometric tests and clinical interviews.

Main Outcome Measures: The presence of vascular risk factors [e.g., high blood pressure (HBP), diabetes mellitus (DM) and dyslipidemia (DLP)] linked to audiometric patterns.

Results: One hundred fifty-six patients (79 women and 77 men) with a mean age of 73.2 ± 10.9 years who were diagnosed with ARHL were studied. A low-frequency audiometric notch at 250 Hz or 500 Hz verified in 36 patients was significantly associated with the presence of HBP, DM or DLP (adjusted OR 3.54, 95% CI: 1.48-8.46, $p<0.001$). Averaged hearing thresholds between 250 and 1000 Hz > 25 dB HL were associated with DM (unadjusted odds ratio 2.97, 95% CI: 1.00-10.6, $p=0.032$). No other association was observed between these thresholds and vascular risk factors.

Conclusions: Low-frequency audiometric notches are related to vascular risk prediction in ARHL patients and merit future attention in larger population studies.

Keywords: Audiometric pattern, age-related hearing loss, cardiocerebrovascular disease**,** vascular risk factors

INTRODUCTION

Age-related hearing loss (ARHL) or presbycusis is hearing loss derived from the degenerative aging process. Its estimated prevalence among elderly individuals ranges between 25% and 80% which makes it the most frequent sensory dysfunction among the elderly (1). The World Health Organization stated ARHL as the most common type of hearing loss, affecting approximately one-third of people over 65 years of age (2). It induces an impairment in speech perception and increases the risks of depression and social isolation (3). The cause of presbycusis remains unclear but is hypothesized to be the result of damage by intrinsic factors such as genetic predisposition, high blood pressure (HBP), diabetes mellitus (DM) and other systemic diseases, and by extrinsic contributors including noise, ototoxic drugs, and diet (3). Degeneration of hair cells, spiral ganglion cells, and the *stria vascularis* was observed in ARHL (4). Based on specific pathological findings in human temporal bones, four separate types of ARHL were defined by Schuknecht: sensory, neural, strial/metabolic and cochlear conductive (5). Consequently, ARHL is likely a multifactorial condition with multiple pathways ending in hearing loss (6).

A graded association between hearing loss and the Framingham Risk Score for cardiovascular risk has been observed (7). In the link between ARHL and cardiovascular risk factors (CVRFs), inflammation seems involved. Chronic inflammation is insidious and remains unnoticed for a long time, which is compatible with the temporal progression of ARHL. Lifestyle options such as sedentarism and an unhealthy diet resulting in weight gain can influence high levels of chronic inflammation in the vascular system (3,5). In a longitudinal population-based cohort study with 1678 participants aged 43–84 years, smoking, central adiposity, and poor glycemic control proved independent predictors of hearing loss (8). In addition, HBP, elevated triglycerides and DM were significantly associated with low-frequency hearing loss (LFHL). Susmano et al. found that 103 patients with ischemic heart disease (IHD) manifested hearing loss up to eight times more than those without IHD (9). They considered LFHL to be an early marker of heart disease. Moreover, Friedland et al. demonstrated a statistically significant relationship between audiometric patterns and the risk of developing vascular disease as well, and considered the strial and low-sloping hearing loss of interest in predicting vascular disease (10). They stated LFHL to be a marker for cardiocerebrovascular disease (CCVD).

The *stria vascularis* is important in vascularization of the organ of Corti and in generation of the endocochlear potential voltages. Decreased vascularization of the auditory system negatively affects hearing by *stria vascularis* dysfunction, resulting in abnormal endolymph

potentials, essential for cochlear hair cell depolarization (11). In animal models, an endolymphatic potential lower than 20 mV provokes “cochlea starving” (11, 12). Vascular diameters vary through the different cochlear turns and can vary more in the apex region, important in the detection of low-frequency sound, than in the basal turn, detecting high-frequency sound (11). Consequently, disturbed cochlear blood flow might contribute to the different patterns observed in ARHL patients. Lars-Göran and Hawkins demonstrated that atrophy of the *stria vascularis* decreases vascularization of the cochlea, which primarily affects the apical and basal segments. The lower endolymph voltage results in poorer hearing function in the low- and high-frequency ranges (13).

In brief, hearing loss of any pattern is associated with CVRFs, probably due to disturbed vascularization, leading to a reduced blood supply. In return, mainly LFHL is linked to myocardial infarction (MI), coronary artery disease (CAD), cerebrovascular accident (CVA), transient ischemic attack (TIA) and HBP (10, 14). Therefore, we hypothesized that specific low-frequency patterns of hearing loss could be predictive of the presence of CVRFs and/or risk of CCVD (MI, CAD, CVA and TIA). Consequently, early identification of this inner ear dysfunction could contribute to the risk assessment of CCVD, allowing improved preventive strategies and early treatment of CCVD. The primary outcome was the assessment of the predictive value of a low-frequency audiometric notch for CVRF presence in ARHL patients. The secondary outcome was the link between audiometric patterns and the presence of CVRFs (HBP, DM, DLP) and CCVD in the same group of ARHL patients.

MATERIALS AND METHODS

Patients and Study Design

We conducted a retrospective chart review of all patients consecutively followed for ARHL by the same ENT physician (JS) between July 2021 and July 2022 at the Hospital Center of Mouscron, Belgium. The routine clinical interview always included questions regarding comorbidities. The electronic health care records were reviewed to collect the following data: demographics, audiometric data, cardiovascular risk factors and previous and current cerebrocardiovascular events. Only patients with a diagnosis of ARHL based on audiometric evaluation were included (symmetric increased hearing thresholds, with air-bone gap 10 decibels (dB HL) or lower and normal middle ear pressure evaluated by tympanometry) (15).

The exclusion criteria included the following: previous otologic surgery, fluctuation in hearing loss, and a history of chronic otitis media, acoustic trauma, suspected ototoxicity, posterior cranial fossa tumors or nasopharyngeal carcinoma.

The assessment of each patient's clinical data was based on full medical documentation. The Institutional Review Board approved the execution of retrospective chart review studies, and the research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patient records and information were anonymized before analysis.

Audiometric testing

Hearing thresholds for air conduction (AC) and bone conduction (BC) were assessed at least once for all patients. The initial test frequency was 1000 Hz. Subsequently, the audiologist tested 2000, 4000, 6000, and 8000 Hz respectively, followed by a retest of 1000 Hz and testing 500, 250, and 125 Hz afterward (16). The pure tone average (PTA4) for AC and BC was determined at 500, 1000, 2000 and 4000 Hz. Pure tone audiometry (GSI AudioStar Pro™) was always performed by the same team of certified clinical audiologists.

Audiometric Pattern Analysis

According to Friedland, distinct patterns of the audiogram (Fig.1 A-D) were identified based on thresholds in low, middle, and high frequencies (10). These patterns were classified as strial, low-sloping, mid-sloping, and high-sloping. The criteria applied for pattern assessment were as follows: (a) high-sloping, ≥ 25 dB HL averaged between 4000 and 8000 kHz with > 15 dB variability and normal thresholds at the lower frequencies of 500 and 1000 Hz; (b) mid-sloping, ≥ 25 dB HL averaged between 2000 and 4000 Hz with > 15 dB variability and normal thresholds at the lower frequencies of 500 and 1000 Hz; (c) low-sloping, ≥ 25 dB HL averaged between 500 and 2000 Hz with > 15 dB variability, (d) strial pattern, ≥ 25 dB HL averaged between 500 and 2000 Hz with ≤ 15 dB variability. A low-frequency notch (either 250 Hz or 500 Hz) was detected in a significant number of audiograms (Fig. 1 E-F).

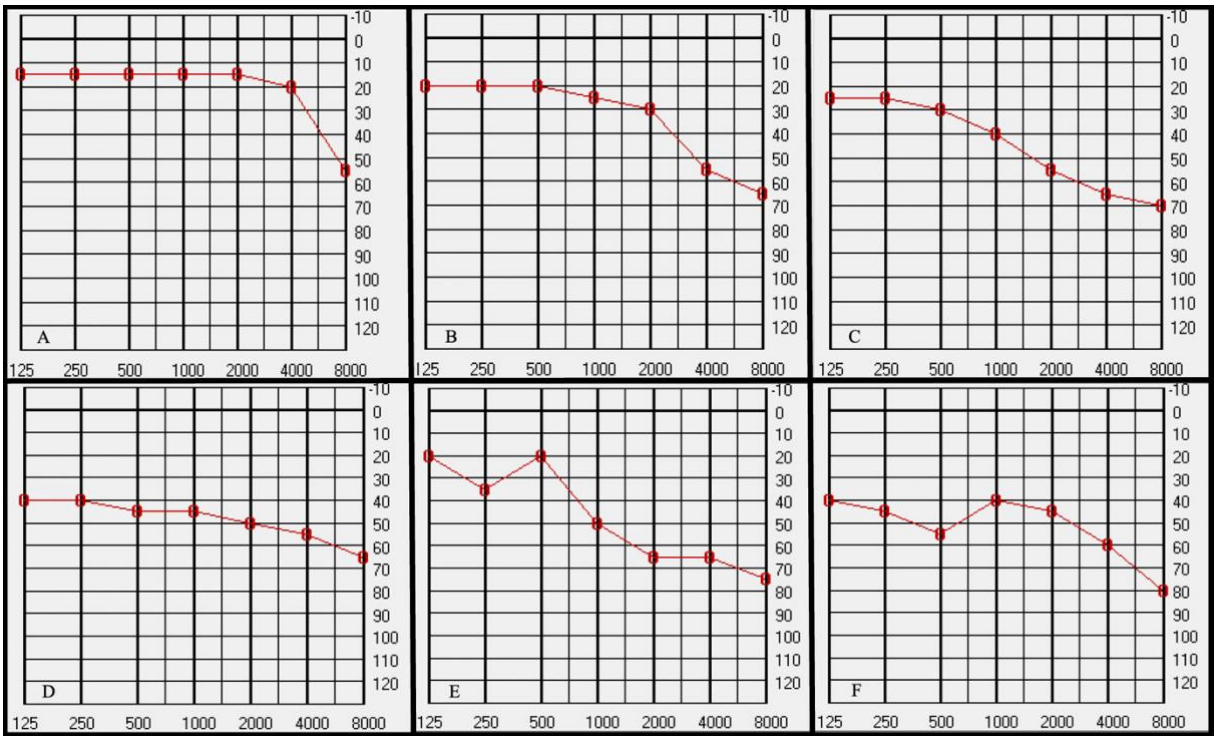
Another audiometric feature assessed in this work was the averaged hearing thresholds for LFHL between 250 and 1000 Hz, as previously reported (8, 19). The hearing thresholds for LFHL were stratified into groups of patients with a mean > 25 dB HL, > 30 dB HL and >40 dB HL.

Comorbidity assessment

During ENT consultation, all patients were questioned about previous comorbidities, including a diagnosis of HBP, DM, DLP and CCVD (CAD and stroke). Moreover, clinical records were analyzed, and HBP was defined when patients were taking antihypertensive

medications, 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, as previously performed (17).

Figure 1. Different audiometric patterns assessed in this study. A) High-sloping, B) Mid-sloping, C) Low-sloping, D) Strial pattern, E) Low-frequency notch at 250 Hz, F) Low-frequency notch at 500Hz.



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.

Statistical Analysis

Data were analyzed by Stata IC16 software (StataCorp LP, College Station, TX, USA). Continuous variables were expressed as the mean ± standard deviation and range, while categorical variables were expressed as frequencies. Contingency table analysis for comparing rates between samples was performed using the chi-squared test or Fisher's exact

test when indicated. Student's *t* test was used to compare means between groups. For all the tests used, a value of $p < 0.05$ was considered significant. To assess the association between specific audiometric patterns and CVRFs, odds ratios and 95% confidence intervals (CIs) were calculated through logistic regression with audiometric patterns as dependent variables and age, sex, HBP, DM, DLP, CCVD, and number of CVRFs as independent variables (DM, HBP, DLP and number of CVRFs were analyzed through different regression analyses to avoid excessive multicollinearity among these variables).

RESULTS

The main characteristics of the 156 included patients are presented in Table 1. Seventy-two patients (46.1%) presented HBP, 27 (17.3%) presented DM and 43 (27.5%) had DLP. Twenty-two patients presented a previous history of CCVD. No significant differences were found in PTA_4 between patients with and without CVRFs or CCVD (p=0.770, p=0.820, respectively, Table 1).

Table 1. Demographic characteristics of subjects included in the study.

	n = 156
Age, years [mean ± SD, range]	73.2 ± 10.9, 46-96
Women [n (%)]	79 (50.6)
Men [n (%)]	77 (49.4)
High Blood Pressure [n (%)]	72 (46.1)
Diabetes Mellitus [n (%)]	27 (17.3)
Dyslipidemia [n (%)]	43 (27.5)
Cardiocerebrovascular disease [n (%)]	22 (14.1)
Stroke [n (%)]	13 (8.3)
Coronary artery disease [n (%)]	9 (5.7)
Pure tone average in all patients (PTA_4, mean ± SD)	45.1 dB HL ± 15
- Patients with at least 1 CVRF (n=80)	45.9 dB HL ± 15.1
- Patients without CVRFs (n=76)	44.1 dB HL ± 16.3
- Patients with previous CCVD (n=22)	47.9 dB HL ± 13.9
- Patients without previous CCVD (n=134)	44.5 dB HL ± 15.9

CCVD, cardiocerebrovascular disease; CVRF, cardiovascular risk factors; PTA_4, pure tone average at 0.5, 1, 2, and 4 kHz; SD, standard deviation

The proposed Friedland's audiometric patterns were not associated with the presence of CVRFs (Table 2).

The low-frequency audiometric notch present in 36 patients was significantly associated with the presence of at least one CVRF (HBP or DM or DLP, unadjusted odds ratio (OR) 3.79, 95% CI: 1.55-9.90, p=0.001, Table 3), and a previous history of stroke showed a trend to the presence of a low-frequency audiometric notch (unadjusted OR 3.23, 95% CI: 0.82-12.07, p=0.039, Table 3). When evaluating the averaged hearing thresholds between 250 and 1000 Hz and its subgroups, positive associations between LFHL averaged hearing threshold > 25 dB HL and DM (unadjusted OR 2.97, 95% CI: 1.00-10.6, p=0.032) were verified. No other association was observed.

Table 2. Friedland's audiometric patterns in ARHL patients with and without CVRFs (HBP, DM and DLP) and CCVD.

Patterns [n (%)]	**with CVRFs**	**without CVRFs**	***p****
Strial (n=69)	37 (23.7)	32 (20.5)	0.602
Low-sloping (n=53)	30 (19.2)	23 (14.7)	0.340
Mid-sloping (n=22)	9 (5.7)	13 (8.3)	0.294
High-sloping (n=12)	4 (2.6)	8 (5.1)	0.238
Patterns [n (%)]	**with CCVD**	**without CCVD**	***p****
Strial (n=69)	11 (7)	58 (37.1)	0.557
Low-sloping (n=53)	10 (6.4)	43 (27.6)	0.220
Mid-sloping (n=22)	1 (0.6)	21 (13.5)	0.317
High-sloping (n=12)	0 (0)	12 (7.7)	0.219

ARHL, age-related hearing loss; CCVD, cardiocerebrovascular disease; CVRF, cardiovascular risk factors; DLP, dyslipidemia; DM, diabetes mellitus; HBP, high blood pressure; * Chi-square test or Fisher Exact test when indicated

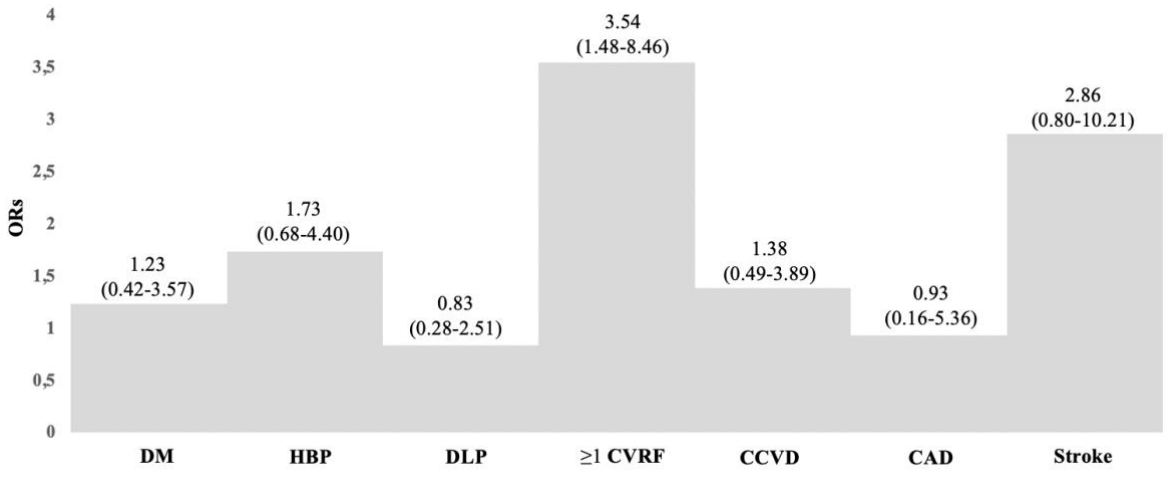
Through multivariable logistic regression considering all factors, a higher risk of any CVRF presence (HBP and/or DM and/or DLP) in ARHL patients was linked to the observation of a low- frequency audiometric notch (adjusted OR 3.54, 95% CI: 1.48-8.46, p<0.001, Fig. 2). No other specific audiometric pattern was associated with the presence of CVRFs or a previous history of CCVD. For instance, the low-sloping pattern presented an adjusted OR of 1.25, 95% CI: 0.62-2.56, p=0.527 for CVRFs and an adjusted OR of 1.49, 95% CI: 0.56-3.99, p=0.421 for a previous history of CCVD, and the strial pattern presented an adjusted OR of 1.22, 95% CI: 0.60-2.45, p=0.581 for CVRFs and an adjusted OR of 0.95, 95% CI: 0.35-2.57, p=0.913 for a previous history of CCVD.

Table 3. Low-frequency audiometric notch in ARHL patients with and without HBP, DM and DLP, and CCVD (CAD and stroke).

CVRF	**Low-frequency audiometric notch**		***p****
[n (%)]	**Yes**	**No**	
HBP (n=72)	21 (13.5)	51 (32.7))	0.095
DM (n=27)	8 (5.1)	19 (12.2)	0.374
DLP (n=43)	12 (7.7)	31 (19.8)	0.377
At least 1 CVRF (HBP and/or DM and/or DLP) (n=80)	27 (17.3)	53 (33.9)	**0.001**
CCVD (n=22)	8 (5.1)	14 (8.9)	0.110
- CAD (n=9)	2 (1.2)	7 (4.4)	0.656
- Stroke (n=13)	6 (3.8)	7 (4.5)	**0.039**

ARHL, age-related hearing loss; CAD; coronary artery disease; CCVD, cardiocerebrovascular disease; CVRF, cardiovascular risk factors; DLP, dyslipidemia; DM, diabetes mellitus; HBP, high blood pressure; * Chi-square test or Fisher Exact test when indicated

Figure 2. Probability (multivariable logistic regression, adjusted odds ratios, 95% confidence interval [95% CI]) of CVRF and CCVD in the presence of a low-frequency audiometric notch. CAD; coronary artery disease; CCVD, cardiocerebrovascular disease; CVRF, cardiovascular risk factor; DLP, dyslipidemia; DM, diabetes mellitus; HBP, high blood pressure; ORs, odds ratios.



DISCUSSION

This exploratory study investigated whether specific low-frequency audiometric patterns can be predictive of the presence of CVRFs and/or CCVD. Additionally, previously proposed

audiometric patterns were explored for a possible link with CVRFs and CCVD in the same group of 156 ARHL patients.

A low-frequency audiometric notch at 250 Hz or 500 Hz present in 36 patients was significantly associated with the presence of HBP, DM or DLP with an unadjusted odds ratio of 3.79 and an adjusted result of 3.54. A previous history of stroke showed a trend toward the presence of a low-frequency audiometric notch, but the large width of the 95% CI prevents definitive conclusions about the association. Friedland's audiometric patterns were not associated with CVRFs or CCVD in our population study. However, our sample size was decidedly inferior to Friedland's population (1168 subjects) (10). A low-frequency audiometric notch > 25 dB HL was associated with the presence of DM (unadjusted odds ratio of 2.97), which matches the previous association between the strial pattern and DM (2,11,18). No other association was observed between these thresholds and risk factors.

Normal cochlear blood flow is a key element for normal auditory transduction (2), and a meta-analysis proposed hypertriglyceridemia and hypercholesterolemia as potential independent risk factors for sudden hearing loss (19). Thus, it is reasonable to propose that factors affecting circulation also worsen hearing. Patients with flat ARHL showed atrophy of the *stria vascularis*, showing that CVRFs can also impact lower frequencies (20, 21). However, specific audiometric notches, as the already familiar noise-induced audiometric notch at high frequencies (22), have not been explored before in LFHL to the best of our knowledge.

Previous works have proposed that LFHL and strial patterns might be linked to CVRFs, including HBP, DM, overweight and DLP (10,11,20,23), but only DM showed this association in our population. Then, specific notches in LFHL could identify preclinical lesions in highly susceptible inner ear regions to vascular suffering, as in the cochlear apex. This could detect high-risk patients for future prevention.

Damage to microvascular endothelial cells could explain the LFHL in DM knowing that this disease can promote other vascular complications, such as peripheral neuropathy, cardiovascular neuropathy, retinopathy and nephropathy (23,24). In 433 ARHL patients, the presence of at least one cardiovascular morbidity was associated with an elevated low-frequency pure-tone average of 42.4 vs. 36.9 dB HL, a difference of 5.47 dB HL (95% CI, 4.15-9.49). These patients also presented accelerated hearing loss (14).

Fisch, Bobozi, and Greig studied internal auditory artery degenerative changes, and a relationship between the perturbed blood supply of the internal auditory artery and the degree of hearing loss was established (25). Moreover, temporal bone analysis has shown that

atrophy of the *stria vascularis* in patients older than 45 to 50 years was present essentially in the middle and apical cochlear turns and that the stria in the basal turn was apparently less prone to atrophy (26).

The present work is based on clinical data from consecutive patients and focuses on a new audiometric notch at low frequencies. However, this study presents limitations starting in 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 relatively small sample size also did not allow solid conclusions.

This exploratory study might be the first reference to introduce low-frequency audiometric notches as a possibility of vascular risk prediction that merits future attention in larger population studies.

REFERENCES

1. Watson N, Ding B, Zhu X, Frisina RD. Chronic inflammation - inflammaging - in the ageing cochlea: A novel target for future presbycusis therapy. *Ageing Res Rev* 2017; 40: 142-148.

2. Engdahl B, Aarhus L, Lie A, Tambs K. Cardiovascular risk factors and hearing loss: The HUNT study. *International Journal of Audiology 2015*; 958-966.

3. Rolim LP, Samelli AG, Moreira RR, et al. Effects of diabetes mellitus and systemic arterial hypertension on elderly patients' hearing. *Braz J Otorhinolaryngol* 2018; 84 (6): 754-763.

4. Kusunoki T, Cureoglu S. Age-related histopathologic changes in the human cochlea [comment]. *Otolaryngol Head Neck Surg*. 2006; 134 (4): 715.

5. Schuknecht HF. *Pathology of the Ear*. Philadelphia: Lea & Febiger, 1993.

6. Hull RH, Kerschen SR. The influence of cardiovascular health on peripheral and central auditory function in adults: a research review. *Am J Audiol*. 2010; 19 (1): 9-16.

7. Tan HE, Lan NSR, Knuiman MW, et al. Associations between cardiovascular disease and its risk factors with hearing loss-A cross-sectional analysis. *Clin Otolaryngol*. 2018; 43 (1): 172-181.

8. Cruickshanks KJ, Nondahl DM, Dalton DS, et al. Smoking, central adiposity, and poor glycemic control increase risk of hearing impairment. *J Am Geriatr Soc.* 2015; 63 (5): 918-24.

9. Susmano A, Rosenbush SW. Hearing loss and ischemic heart disease. *Am J Otol* 1988; 9: 403–408.

10. Friedland DR, Cederberg C, Tarima S. Audiometric pattern as a predictor of cardiovascular status: Development of a model for assessment of risk. *Laryngoscope* 2009; 119: 473–486.

11. Bertrand RA, Huang Z. Association between audiometric patterns and probabilities of cardiovascular diseases. *Laryngoscope Investig Otolaryngol* 2018; 30 (6): 478-485.

12. Morizane I, Hakuba N, Shimuzu Y, et al. Transient cochlear ischemia and its effects on the stria vascularis. *Neuroreport* 2005; 16: 799–802.

13. Lars-Göran J, Hawkins JE Jr. Symposium on basis ear research. II. Strial atrophy in clinical and experimental deafness. *Laryngoscope* 1972; 82: 1105–1125.

14. Wattamwar K, Qian ZJ, Otter J, et al.Association of Cardiovascular Comorbidities With Hearing Loss in the Older Old. *JAMA Otolaryngol Head Neck Surg*. 2018; 144 (7): 623-629.

15. Lowell SH, Paparella MM. Presbycusis: what is it? *Laryngoscope* 1977; 87: 1710–1717.

16. American Speech-Language-Hearing Association. Guidelines for manual pure-tone threshold audiometry [Guidelines]. Available from www.asha.org/policy. Accessed Septembre 29, 2022.

17. Marcucci R, Alessandrello Liotta A, Cellai AP, et al. Cardiovascular and thrombophilic risk factors for idiopathic sudden sensorineural hearing loss. *J Thromb Haemost* 2005; 3 (5): 929-934.

18. Horikawa C, Kodama S, Tanaka S, et al. Diabetes and risk of hearing impairment in adults: A meta-analysis. *J Clin Endocrinol Metab*. 2013; 98: 51–58.

19. Simões J, Vlaminck S, Seiça R, Acke F, Miguéis A. Cardiovascular Risk and Sudden Sensorineural Hearing Loss: A Systematic Review and Meta-Analysis. *Laryngoscope*. 2022; 10.1002/lary.30141. Advance online publication.

20. Schuknecht HF. Further observations on the pathology of presbycusis. *Arch Otolaryngo.* 1964; 80: 369–382.

21. Gates GA, Cobb JL, D'agostino RB, Wolf PA. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. *Arch Otolaryngol Head Neck Surg*. 1993; 119: 156–161.

22. Gates GA, Schmid P, Kujawa SG, Nam B, D'Agostino R. Longitudinal threshold changes in older men with audiometric notches. Hear Res. 2000; 141 (1-2): 220-8.

23. Lebech Cichosz S, Hejlesen O. Association between diabetes and changes in hearing: A cross-sectional study. *Diabetes Metab*. 2018; 44 (1): 87-90.

24. Friedman S, Schulman R, Weiss S. Hearing and diabetic neuropathy. *Arch Intern Med.* 1975; 135: 573–6.

25. Fisch, U, Bobozi, M, Greig D. Degenerative changes of the arterial vessels of the internal auditory meatus during the process of aging. *Acta Otolaryngologica*. 1972; 73: 259–266.

26. Johnsson LG, Hawkins JE Jr. Vascular changes in the human inner ear associated with aging. *Ann Otol Rhinol Laryngol*. 1972; 81 (3): 364-76.

Additional Results

1. Does cardiovascular risk influence caloric weakness in acute unilateral peripheral vestibulopathy (AUPVP)?

From the same source population and in the subgroup of AUPVP patients it was hypothesized if the cardiovascular risk could influence the severity of caloric weakness.

To accomplish this analysis, AUPVP patients were divided into groups according to the presence or not of CVRFs (DM, HBP, and DLP). Then, the means of caloric deficit were calculated for each group and compared (Table XI).

Table XI. Caloric weakness analysis between AUPVP patients with and without CVRFs.

	DM	**HBP**	**DLP**
	Yes/No	**Yes/No**	**Yes/No**
Caloric weakness (%)	81/57	63/61	61/63
*P**	**0.03**	>0.05	>0.05

Abbreviations: DM – diabetes mellitus; HBP – high blood pressure; DLP-Dyslipidemia* student t test;

Only DM significantly influenced the caloric weakness in AUPVP patients, with a weaker result in DM patients ($p<0.05$). There were no significant differences in caloric weakness regarding the presence or absence of CCVD and no correlation with the number of CVRFs.

2. Does cardiovascular risk influence the degree of hearing loss or the hearing loss pattern in SSNHL?

From the same source population of article number 3 and in the subgroup of SSNHL patients, it was hypothesized whether that cardiovascular could influence the degree of hearing loss and the type of audiometric curve. Pure tone audiometry (frequencies 125, 250, 500, 1000, 2000, 4000, and 8000 Hz) was performed in all patients (GSI AudioStar Pro™). The audiometric pattern was established according to the Sheehy classification (90). Thus, audiograms were divided into 4 patterns: low tone, high tone, flat tone, and total hearing loss types. Also, the severity of hearing loss was evaluated through the average of the auditory

thresholds in five frequencies (250, 500, 1000, 2000, and 4000 Hz). The severity was categorized into mild (hearing loss of 40 dB or less), moderate (hearing loss of more than 40 dB but not exceeding 70 dB), severe (hearing loss of more than 70 dB but not exceeding 90 dB), and profound (hearing loss of more than 90 dB).

The means of hearing loss and audiometric patterns were established for each CVRF group and compared (Table XII).

Table XII. Audiometric patterns in SSNHL patients with and without CVRFs.

Pattern	**SSNHL with CVRFs**	**SSNHL without CVRFs**	***p***
	n	**n**	
Low tone	8	3	>0.05
High tone	11	12	>0.05
Flat	8	5	>0.05
Total	1	1	>0.05

Patients with at least one CVRF presented a PTA of 56 dB ± 5 (range from 46 to 66), and with no CVRF, a PTA of 49 dB ± 5 (range from 39 to 58). However, this tendency to more severe SSNHL in DM patients was not statistically significant. There were no significant differences in PTA regarding the presence or absence of CCVD and no correlation with the number of CVRFs.

Discussion

1. General Discussion

The work performed in this thesis allowed to explore both acute and chronic events of the inner ear and their link with vascular risk and CCVD.

Regarding AUPVP, the published review identified essential gaps in the literature regarding exploring vascular etiology in AUPVP. No cohort studies with a control group were found, unlike SSNHL studies. Similarly, no studies were identified in this search regarding the risk of future vascular events (stroke and myocardial infarction) compared to the works available for SSNHL. Thereby, this stimulated the analysis of AUPVP with a matched control group.

The pathophysiology of AUPVP needs further exploration concerning the role of viral inflammation and vascular events in the vestibular organ, with significant clinical implications. Acute vertigo may occur due to a labyrinth infarction. However, current imaging techniques do not readily allow the identification of isolated labyrinthine infarctions as a cause of acute audiovestibulopathy (22). The published systematic review presented in this thesis concerning vascular mechanisms of AUPVP showed exciting findings. Our first observation is that comparing results remains challenging due to the various terms used in different studies. Only recently, the literature has shifted to AUPVP (20).

Furthermore, it is relevant to discuss the clinical signs in patients with an AICA stroke diagnosis showing isolated otovestibular dysfunction (vertigo, hearing loss, and/or tinnitus) with normal MRI imaging one to 10 days before the appearance of neurological symptoms (29). Early signs may be caused by early smaller emboli deeper in the AICA vascular territory, namely the inner ear microcirculation. Supportive information is the histopathology findings showing vascular occlusion in ARHL patients probably more prone to vascular accidents (34,40). Moreover, several cases of labyrinthine infarction have been linked to cardioembolism (72-75), and isolated deafness has also been reported during the embolization of a meningioma (76) or cardiopulmonary bypass surgery (77). Besides, artery-to-artery embolism is another mechanism of labyrinthine infarction (78). Each labyrinth compartment may be selectively involved when embolism involves a specific branch of the LA, causing isolated vertigo or hearing loss. For example, isolated vertigo may occur without hearing loss

when the anterior vestibular artery is only involved. Hearing loss may be an isolated finding when the common cochlear artery is selectively affected (79). Consequently, the clinical assessment of dizziness/vertigo patients, including accompanied neurological symptoms and signs, the presence of vascular risk factors, and findings of ocular motor examination, is likely to differentiate between central and peripheral etiologies but might also indicate the eventual origin of AUPVP etiology. We should then attempt to detect MRI infarctions in other territories apart from AICA (79).

Regarding the neutrophil-to-lymphocyte ratio (NLR), interesting evidence points to a vascular origin of AUPVP. Oh *et al.* and Şahin *et al.* found NLR to be significantly higher in the AUPVP patients than in the controls (80,81). These findings suggest a neutrophil-mediated immune pathway in developing AUPVP by mediating inflammatory and thrombotic changes in the vestibular organ. Indeed, viral infections usually increase the lymphocyte count and decrease neutrophil counts, leading to lower NLR values (82). Similar results were found in sudden sensorineural hearing loss (83,84). However, regarding MPV (mean platelet volume) studies, Beyan and Beyan doubted this hypothesis, arguing that MPV-related research was hampered by the differences in MPV measurement standardization leading to variable results (85).

As a non-modifiable CVRF, aging showed no effect on spontaneous recovery and the need for vestibular rehabilitation (86). In contrast, other CVRFs were statistically associated with AUPVP (87). Another argument for a specific pathogenetic mechanism in AUPVP is the comparison to Bell's Palsy. Commonly, AUPVP is approached analogous to Bell's palsy, but significant differences exist. First, corticosteroids are effective in treating Bell's palsy, while their effect in AUPVP is less established (88). This might suggest a different mechanism rather than a similarity. Then, benign paroxysmal positional vertigo (BPPV) is more prevalent in patients with a history of AUPVP (20% of patients will develop BPPV in their lifetime (89), which also supports a pathogenetic model with involvement of an intralabyrinthine lesion rather than a neuritis hypothesis (90).

Concerning SSNHL, the assessed evidence from 21 studies (102292 SSNHL patients) and the quantitative analysis from seven studies to assess the link between CVRFs and SSNHL showed that hypertriglyceridemia might be an independent risk factor for SSNHL, increasing the risk 1.54-fold. After sensitivity analysis, hypercholesterolemia was also presented as a potential independent risk factor for SSNHL.

Sudden sensorineural hearing loss is a diagnostic challenge as various mechanisms were proposed, but no underlying disease is frequently found. Recently, the association between

migraine and SSNHL was analyzed in a meta-analysis. Migraine was associated with a 1.8-fold increased risk of developing SSNHL, exploring the possibility of a vascular etiology in SSNHL (91). Otherwise, recent works indicated that SSNHL might be an independent risk factor for stroke development, especially in elderly patients (47). In fact, cochlear microvascular disorders relate to plasma viscosity and thrombotic events. Therefore, the proposed mechanism was that lipotoxicity of blood vessels inducing atherosclerotic changes with endothelial injury, resulting in cochlear microangiopathy with decreased blood supply (44). Ullrich *et al.* (92) and Ballesteros *et al.* (93) found an identical frequency of CVRFs between controls and SSNHL patients.

Conversely, this thesis shows that many studies showed conflicting results (Article number 2). These studies' limitations remain in their retrospective analysis, relatively small population sizes, univariate analysis, lack of longitudinal data, and no standardized verification of the diagnosis with audiometric data. In addition, studies evaluating lipids levels did not use the same threshold concentrations to define pathology.

A systematic review and meta-analysis of the risk factors for SSNHL from 2012 concluded that smoking (OR of 1.34; 95% CI 1.12-1.61) and heavy alcohol consumption (OR of 2.21; 95% CI 1.68-2.91) appeared to be associated with a higher risk of developing SSNHL, but no significant association was found for HBP and DM (42). Nonetheless, the cohort study of Lin *et al.* found a higher risk of SSNHL in DM patients (OR 1.59; 95% CI 1.29-1.96) (94). Previously, pooled results were only possible for TC and LDL-c without significant findings. In the present thesis, collected evidence from inception to 2021 has already allowed overall results for more CVRFs such as TG and more precise results for TC in the sensitivity analysis. These results were not described in a meta-analysis until now. Other parameters have been implied in the development of SSNHL as MTHFR enzyme polymorphisms (42,43,45), factor V Leiden and factor VIII mutations (42,43,45), neutrophil/lymphocyte ratio, and platelets/lymphocyte ratio (83,84). However, the results are not consistent (42-45).

The novelty of the performed approach for the case-control analysis presented in article number 3 is the study of different manifestations of inner ear hypofunction from the same source population instead of different methods in diverse populations. This study investigates the prevalence of DM, HBP, and DLP in AUIEH patients compared to matched controls and the influence of the number of CVRFs in AUIEH occurrence. Previous CCVD was also analyzed in cases and controls. A subgroup analysis was performed to evaluate if differences occurred between the three groups of inner ear acute disease. Overall, all assessed CVRFs were more prevalent in the AUIEH group when compared to controls, and a tendency to

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). Only previous CCVD individually predicted AUIEH (OR 8.41; 95% CI 2.36-29.88) of all variables considered in multivariable conditional logistic regression. Subgroup analysis showed that results were equivalent in AUPVP and SSNHL, with a statistically significant tendency to disease 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).

Previously, other works verified a higher prevalence of CVRFs in AUPVP and SSNHL. 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 compared to the general population, however, no matched controls were used. Instead, the ratio of CVRFs among patients was compared to those among the general Israeli population (87). However, Han et al. did not find significant differences regarding HBP, DM, and DLP between AUPVP patients and controls. Nevertheless, the prevalence of carotid plaques was significantly higher in AUPVP patients (95). However, this study has a significant limitation: since it was considered a ratio of less than 1:1 between controls and patients (74 controls for 90 patients). Chung *et al.* showed that higher metabolic syndrome scores are associated with developing AUPVP. Still, a ratio less than 1:1 between controls and patients was considered, in addition to smaller population size (58 AUPVP patients) (96). The design and sample size of article number 3 may provide more substantiated data for research on the link between CVRFs and AUPVP. Indeed, further studies on vascular dysfunction in AUPVP are crucial particularly after the surprising results that showed that the pattern of the vestibular lesion pattern observed in AUPVP is inconsistent with an isolated nerve lesion (90).

Regarding SSNHL, previous studies from large-scale population administrative databases provided evidence for a higher prevalence of CVRFs in SSNHL patients (94,97-99), and article number 2 of this thesis proposed hypertriglyceridemia and hypercholesterolemia as potential independent risk factors for SSNHL (55).

A recent inner ear vascular entity was proposed for acute audiovestibular deficit based on VEMPs and vHIT testing. The vestibulocochlear syndrome could explain the clinical presentation of SSNHL at high frequencies with normal hearing or mild hearing loss at low and middle frequencies, hypofunction of the posterior semi-circular canal with the preserved function of the lateral and anterior canals, and normal saccule function (100,101). In this context, selective inner ear ischemia will explain these combinations because the

vestibulocochlear artery branches to the posterior vestibular artery and the cochlear branch. Then, it is responsible for the blood supply of the basal turn of the cochlea, posterior semi-circular canal, and saccule. However, the saccule can be spared because it also receives blood supply from the AVA. If viral etiology is suspected, the saccule should be affected due to the expansion of viral labyrinthitis to the posterior semi-circular canal from the cochlea and that must involve the saccule (100).

Indeed, these recent descriptions confirm the possibility of selective inner ear vascular damage with specific vestibular and audiometric patterns, which motivated the same rationale in ARHL. In article number 4, a low-frequency audiometric notch at 250 Hz or 500 Hz present in 36 patients was significantly associated with the presence of HBP, DM, or DLP with an unadjusted odds ratio of 3.79, 95% CI: 1.55-9.90, p=0.001) and an adjusted result of 3.54, 95% CI: 1.48-8.46, p<0.001. A previous history of stroke showed a trend toward the presence of a low-frequency audiometric notch, but the ample width of the 95% CI prevents definitive conclusions about the association.

Friedland's audiometric patterns were not associated with CVRFs or CCVD in our population study. However, our sample size was decidedly inferior to Friedland's population (1168 subjects) (59). An LFHL > 25 dB HL was associated with the presence of DM (unadjusted odds ratio of 2.97, 95% CI: 1.00-10.6, p=0.032), which matches the previous association between the strial pattern and DM (58,102,103). No other association was observed between these thresholds and risk factors.

Normal CoBF is an essential element for normal auditory transduction (102). Thus, it is reasonable to propose that factors affecting circulation also worsen hearing. Patients with flat ARHL showed atrophy of the *stria vascularis*, showing that CVRFs can also impact lower frequencies (104,105). However, specific audiometric notches, such as the familiar noise-induced audiometric notch at high frequencies (106), have yet to be explored in LFHL.

Previous works have proposed that LFHL and strial patterns might be linked to CVRFs, including HBP, DM, being overweight, and DLP (58,59,104,107), but only DM showed this association in the population studied for this thesis. Then, specific notches in LFHL could identify preclinical lesions in highly susceptible inner ear regions to vascular suffering, as in the cochlear apex. This could detect high-risk patients for future prevention.

Damage to microvascular endothelial cells could explain the LFHV in DM, knowing that this disease can promote other vascular complications, such as peripheral neuropathy, cardiovascular neuropathy, retinopathy, and nephropathy (107,108). In 433 ARHL patients, at least one cardiovascular morbidity was associated with an elevated low-frequency pure-tone

average of 42.4 vs. 36.9 dB HL, a difference of 5.47 dB HL (95% CI, 4.15-9.49). These patients also presented accelerated hearing loss (109).

Fisch, Bobozi, and Greig studied degenerative changes in the LA, and a relationship between perturbed blood supply and the degree of hearing loss was established (110). Moreover, temporal bone analysis in patients older than 45 showed that atrophy of the *stria vascularis* was more critical in the middle and apical cochlear turns and that the stria in the basal turn was less prone to atrophy (7). The strial network is also widest and most complex near the basal end and becomes narrower and simpler towards the apex (7).

Animal models also support microvascular degeneration in ARHL. The C57BL/6 mice are a well-studied model of ARHL, from age six months onward, demonstrating progressive high-to-low frequency hearing loss with age (111,112). Like humans, histopathological alterations are first seen in the basal turn, which progress to the apical turns as these animals first lose their OHC and later IHC (113). Older animals had a significantly decreased area of the *strial vascularis*, and there was a significant decrease in basal to apical strial area (28%). Indeed, when normalizing for the strial area, the area containing blood vessels was significantly decreased in older animals and had a significantly increased apical lumen size compared to young animals (113).

Research on this topic is of paramount importance as it could clarify the possible presence of higher vascular risk in selective patients with inner ear dysfunction. Registering clinical background and CVRFs seems a simple and valuable step in this matter. Adjunctive tests such as vHIT and VEMPs can detect a specific lesion pattern in the five components of the vestibular system, which might be critical to clarify the viral hypothesis or the presence of a vascular insult. When a high suspicion of vascular origin is present, a cardiovascular assessment seems a reasonable approach to be suggested.

2. Limitations and Future Perspectives

The ARHL study is based on clinical data from consecutive patients and focuses on a new audiometric notch at low frequencies. However, this study presents limitations starting with its retrospective nature. In addition, only three CVRFs were analyzed. The relatively small sample size also did not allow solid conclusions. Nonetheless, this exploratory study might be the first reference to introduce low-frequency audiometric notches as a possible vascular risk predictor that merits future attention in more extensive population studies.

Other limitations should be highlighted for the performed studies. There is some variation in the definition of AUPVP in the review presented in article number 1, which poses a challenge when trying to compare studies from different authors or clinics. Indirect arguments provided in recent literature sustain some evidence for vascular mechanisms. However, most studies are retrospective in their analysis, with relatively small sample sizes and limited data regarding the control group. More extensive prospective studies of AUPVP patients could lead to a better diagnostic work-up and more precise therapy.

Another critical point is that the best available evidence is from large-scale population administrative databases, which can be susceptible to administrative inconsistencies. Finally, the heterogeneity of pooled studies in the SSNHL meta-analysis was distributed between 0 and 97%, announcing a variability in studies. This should be considered before incorporating results into clinical practice. A methodological effort was made to address potential sources of bias in article number 3, namely from the control group. However, the study of acute inner ear events presents other limitations due to its retrospective nature. In addition, only three CVRFs were analyzed when factors like smoking, obesity, physical inactivity, and types of DLP could also influence results. The small sample size of AUAVH did not allow solid conclusions.

The described findings should encourage extensive, clinical-based, multi-center prospective studies assessing the link between inner ear acute events and vascular risk to neutralize the limitations found in this work and the literature. Future research should focus on identifying high-risk patients that would benefit from secondary prevention for vascular disease. Until now, there is no imaging marker for inner ear ischemia. This step would confirm the hypothesis proposed in this thesis in an expeditious way that could influence vestibular and auditory outcomes, but also reduce the odds of important vascular events in the future.

Finally, a deep understanding of the cochlear blood flow regulation in humans should be acquired to clarify how CVRFs may influence it and how its variation could trigger inner ear dysfunction. In addition, control of this mechanism could allow a more efficient

pharmacological management of various inner ear diseases poorly understood until the present time.

Conclusion

Long-term, multi-center, and prospective studies are crucial to clarify the link between CVRFs, SSNHL, AUPVP, and ARHL. Currently, medical imaging cannot prove ischemic events in the inner ear, but if this barrier is exceeded, further evidence can be added. Our results showed that hypertriglyceridemia and hypercholesterolemia might be independent risk factors for SSNHL, increasing the risk 1.54-fold and 2.09-fold, respectively. A diagnostic standardization in patients with SSNHL is needed regarding cardiovascular comorbidities. The risk factors may be well investigated to develop more evidence on etiologic incidents. Regarding the vascular origin of SSNHL, we can conclude that there is contradictory evidence on this etiology: SSNHL probably is a predominantly multifactorial disease. Still, a specific group of high vascular-risk patients may be more susceptible.

Acute unilateral inner ear hypofunction patients presented more CVRFs when compared to controls, and the presence of two or more CVRFs predicted acute inner ear hypofunction. The results tendency was consistent when analyzing subgroups of AUPVP and SSNHL. The vascular risk present in these identities may indicate a possible identical vascular mechanism with different inner ear manifestations. However, caution on results interpretation is needed considering the limitations of our study.

If future studies show that SSNHL and AUPVP may reveal unknown vascular risks, this will have important implications for therapeutic and preventive strategies.

An association between a low-frequency audiometric notch and the presence of at least 1 CVRF between HBP, DM, and DLP was observed, suggesting that specific cochlear apical regions could be more prone to vascular insult. This audiometric feature may potentially identify vascular risk, but the precision of the presented estimates is low. Thus, additional studies are needed.

Key messages

1. Hypertriglyceridemia may be an independent risk factor for SSNHL, increasing the risk 1.54-fold. After sensitivity analysis, hypercholesterolemia was also presented as a potential independent risk factor for SSNHL.

2. Cardiovascular risk factors were more prevalent in the AUIEH group compared to controls, and a tendency to 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).

3. In multivariable conditional logistic regression, previous CCVD individually predicted AUIEH (OR 8.41; 95% CI 2.36-29.88).

4. Subgroup analysis showed that results were equivalent in AUPVP and SSNHL, with a statistically significant tendency to disease 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).

5. The presence of DM significantly influenced caloric weakness in AUPVP patients, with a weaker result in DM patients ($p<0.05$). There were no significant differences in caloric weakness regarding the presence or absence of CCVD and no correlation with the number of CVRFs.

6. The low-frequency audiometric notch present in 36 patients was significantly associated with the presence of at least one CVRF (HBP or DM or DLP, unadjusted OR 3.79, 95% CI: 1.55-9.90 and adjusted OR 3.54, 95% CI: 1.48-8.46).

References

1) Miguéis AC, Lavrador, JP. Sistema Auditivo e Vestibular. Manual de Anatomia Humana Para Estudantes. Prime Books; 2020. p. 685-700.

2) Runge C, Friedland D. Anatomy of the Auditory System. Cummings. Elsevier; 2015. p. 1987-1993.

3) Mazzoni A. The vascular anatomy of the vestibular labyrinth in man. Acta Otolaryngol Suppl 1990; 472: 1-83. doi: 10.3109/00016489009121137.

4) Axelsson A. The vascular anatomy of the cochlea in the guinea pig and in man. Acta Otolaryngol. 1968; 3: Suppl. 243.

5) Nakashima T, Naganawa S, Sone M, *et al*. Disorders of cochlear blood flow. Brain Res 2003; 43: 17-28. doi: 10.1016/s0165-0173(03)00189-9.

6) Wangemann P, Liu J. Osmotic water permeability of capillaries from the isolated spiral ligament: new in-vitro techniques for the study of vascular permeability and diameter. Hear. Res. 1996; 95: 49-56. doi: 10.1016/0378-5955(96)00007-x.

7) Shi X. Physiopathology of the cochlear microcirculation. Hear Res. 2011; 282 (1-2): 10-24. doi: 10.1016/j.heares.2011.08.006. Epub 2011 Aug 23.

8) Brechtelsbauer PB, Ren TY, Miller JM, *et al*. Autoregulation of cochlear blood flow in the hydropic guinea pig. Hear Res. 1995; 89: 130-136. doi: 10.1016/0378-5955(95)00130-4.

9) Brown JN, Nuttall AL. Autoregulation of cochlear blood flow in guinea pigs. Am J Physiol. 1994; 266: 458-467. doi: 10.1152/ajpheart.1994.266.2.H458.

10) Ruan RS. Possible roles of nitric oxide in the physiology and pathophysiology of the mammalian cochlea, Ann. NY Acad. Sci. 2002; 962: 260–274. doi: 10.1111/j.1749-6632.2002.tb04073.x.

11) Takumida M, Anniko M. Direct evidence of nitric oxide production in the guinea pig organ of Corti. Acta Otolaryngol. 2001; 121: 342–345. doi: 10.1080/000164801300102716.

12) Michel O, Hess A, Bloch W, *et al*. Localization of the NO/cGMP-pathway in the cochlea of guinea pigs. Hear. Res.1999; 133: 1–9. doi: 10.1016/s0378-5955(99)00049-0.

13) Michel O, Hess A, Su J, *et al*. Expression of inducible nitric oxide synthase (iNOS/NOS II) in the hydropic cochlea of guinea pigs. Hear. Res. 2000; 143: 23–28. doi: 10.1016/s0378-5955(00)00018-6.

14) Tsuji S, Tabuchi K, Hara A, *et al*. Long-term observations on the reversibility of cochlear dysfunction after transient ischemia. Hear. Res. 2002; 166: 72–81. doi: 10.1016/s0378-5955(02)00299-x.

15) Watanabe K, Inai S, Jinnouchi K, *et al*. Nuclear-factor kappa B (NF-kappa B)-inducible nitric oxide synthase (iNOS/NOS II) pathway damages the stria vascularis in cisplatin-treated mice. Anticancer Res. 2002; 22: 4081–4085.

16) Inafuku S, Wu M, Kimura M, *et al*. Immunohistochemical demonstration of inducible nitric oxide and nuclear factor-kappa B with reference to age-related changes in the mouse spiral and vestibular ganglion. Okajimas Folia Anat. Jpn. 2000; 77: 125–131. doi: 10.2535/ofaj1936.77.4_125.

17) Kong WJ, Ren T, Nuttall AL. Electrophysiological and morphological evaluation of the acute ototoxicity of sodium nitro-prusside. Hear. Res. 1996; 99: 22–30. doi: 10.1016/s0378-5955(96)00076-7.

18) Brechtelsbauer B, Nuttall AL, Miller JM. Basal nitric oxide production in regulation of cochlear blood flow. Hear. Res. 1994; 77: 38–42. doi: 10.1016/0378-5955(94)90251-8.

19) Nagura M, Iwasaki S, Mizuta K, *et al*. Role of nitric oxide in focal microcirculation disorder of guinea pig cochlea. Hear. Res. 2001; 153: 7–13. doi: 10.1016/s0378-5955(00)00250-1.

20) Kim JS, Lee H. Inner ear dysfunction due to vertebrobasilar ischemic stroke. Semin Neurol 2009; 29: 534-540. doi: 10.1055/s-0029-1241037.

21) Goebel JA, O'Mara W, Gianoli G. Anatomic considerations in vestibular neuritis. Otol Neurotol 2001; 22: 512-518. doi: 10.1097/00129492-200107000-00018.

22) Strupp M, Mandalà M, López-Escámez JA. Peripheral vestibular disorders: an update. Curr Opin Neurol 2019; 32: 165-173. doi: 10.1097/WCO.0000000000000649.

23) Rujescu D, Hartmann AM, Giegling I, *et al*. Genome-wide association study in vestibular neuritis: involvement of the host factor for HSV- 1 replication. Front Neurol 2018; 20: 591. doi: 10.3389/ fneur.2018.00591.

24) Jeong SH, Kim HJ, Kim JS. Vestibular neuritis. Semin Neurol 2013; 33: 185-194. doi: 10.1055/s-0033-1354598.

25) Hegemann SCA, Wenzel A. Diagnosis and treatment of vestibular neuritis/neuronitis or peripheral vestibulopathy (PVP)? Open questions and possible answers. Otol Neurotol 2017; 38: 626-631. doi: 10.1097/MAO.000000000000139.

26) Neuhauser HK. The epidemiology of dizziness and vertigo. Handb Clin Neurol 2016; 137: 67-82. doi: 10.1016/ B978-0-444-63437-5.00005-4.

27) Muelleman T, Shew M, Subbarayan R, *et al*. Epidemiology of dizzy patient population in a neurotology clinic and predictors of peripheral etiology. Otol Neurotol 2017; 38: 870-875. doi: 10.1097/ MAO.0000000000001429.

28) Fife TD, Colebatch JG, Kerber KA, *et al*. Practice guideline: cervical and ocular vestibular evoked myogenic potential testing: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2017; 89: 2288-2296. doi: 0.1212/ WNL.0000000000004690.

29) Kim HA, Lee H. Recent advances in understanding audiovestibular loss of a vascular cause. J Stroke 2017; 19: 61-66. doi: 10.5853/jos.2016.0085.

30) Hilton R. Acute renal failure. BMJ 2006; 333: 786-790. doi: 10.1136/bmj.38975.657639.AE

31) Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep 2017; 14: 385-392. doi: 10.1007/s11897-017-0351-y.

32) Feroze KB, O'Rourke MC. Transient loss of vision. Treasure Island (FL): StatPearls Publishing 2020. https://www.ncbi.nlm.nih.gov/ books/NBK430845/

33) Mei X, Atturo F, Wadin K, *et al*. Human inner ear blood supply revisited: the Uppsala collection of temporal bone-an international resource of education and collaboration. Ups J Med Sci 2018; 123: 131-142. doi: 10.1080/03009734.2018.1492654.

34) Cruickshanks KJ, Nondahl DM, Dalton DS, *et al*. Smoking, central adiposity, and poor glycemic control increase risk of hearing impairment. J Am Geriatr Soc 2015; 63: 918-924. doi: 10.1111/ jgs.13401.

35) Chandrasekhar SS, Tsai Do BS, Schwartz SR, *et al*. Clinical practice guideline: sudden hearing loss (update). Otolaryngol Head Neck Surg. 2019; 161(1_suppl): S1-S45. doi: 10.1177/0194599819859885.

36) Gündogan F, Bayram A, Kalkan M, *et al*. Plasma levels of endothelial cell-specific molecule-1 and pentraxin-3 in idiopathic sudden sensorineural hearing loss. J Laryngol Otol. 2018; 132: 1-5. doi: 10.1017/S002221511800186X.

37) Chen X, Fu YY, Zhang TY. Role of viral infection in sudden hearing loss. J Int Med Res. 2019; 47(7): 2865-2872. doi: 10.1177/0300060519847860.

38) Kim C, Sohn JH, Jang MU, *et al*. Ischemia as a potential etiologic factor in idiopathic unilateral sudden sensorineural hearing loss: analysis of posterior circulation arteries. Hear Res. 2016; 331: 144-151. doi: 10.1016/j.heares.2015.09.003.

39) Kobiyama K, Ley K. Atherosclerosis. Circ Res. 2018; 123(10): 1118-1120. doi: 10.1161/CIRCRESAHA.118.313816.

40) Fischer ME, Schubert CR, Nondahl DM, *et al*. Subclinical atherosclerosis and increased risk of hearing impairment. Atherosclerosis. 2015; 238(2): 344-349. doi: 10.1016/j.atherosclerosis.2014.12.031.

41) Balakumar P, Maung UK, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacol Res. 2016; 113: 600-609. doi: 10.1016/j.phrs.2016.09.040.

42) Lin RJ, Krall R, Westerberg BD, *et al*. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. Laryngoscope. 2012; 122: 624-635. doi: 10.1002/lary.22480.

43) Passamonti SM, Di Berardino F, Bucciarelli P, *et al*. Risk factors for idiopathic sudden sensorineural hearing loss and their association with clinical outcome. Thromb Res. 2015; 135: 508-512. doi: 10.1016/j.thromres.2015.01.001.

44) Fasano T, Pertinhez TA, Tribi L, *et al*. Laboratory assessment of sudden sensorineural hearing loss: a case–control study. Laryngoscope. 2017; 127: 2375-2381. doi: 10.1002/lary.26514.

45) Fusconi M, Chistolini A, de Virgilio A, *et al*. Sudden sensorineural hearing loss: a vascular cause? Analysis of prothrombotic risk factors in head and neck. Int J Audiol. 2012; 51: 800-805. doi: 10.3109/14992027.2012.705904.

46) Lin HC, Chao PZ, Lee HC. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. Stroke. 2008; 39 (10): 2744-2748. doi: 10.1161/STROKEAHA.108.519090.

47) Lammers MJW, Young E, Westerberg BD, *et al*. Risk of stroke and myocardial infarction after sudden sensorineural hearing loss: a meta-analysis. Laryngoscope. 2021; 131 (6): 1369-1377. doi: 10.1002/lary.29237.

48) Crowson MG, Mulder H, Cyr DD, *et al*. Idiopathic sudden sensorineural hearing loss is not a sentinel event for acute myocardial infarction. Otol Neurotol. 2018; 39 (7): e518-e523. doi: 10.1097/MAO.0000000000001868.

49) Quaranta N, De Ceglie V, D'Elia A. Endothelial dysfunction in idiopathic sudden sensorineural hearing loss: a review. Audiol Res. 2016; 6 (1): 151. doi: 10.4081/audiores.2016.151.

50) Fisch U, Dobozi M, Greig D. Degenerative changes of the arterial vessels of the internal auditory meatus during the process of aging. A histological study. Acta Otolaryngol. 1972; 73 (2): 259-266. doi: 10.3109/00016487209138940.

51) Fusconi M, Attanasio G, Capitani F, *et al*. Is there a relation between sudden sensorineural hearing loss and white matter lesions? Eur Arch Otorhinolaryngol. 2019; 276 (11): 3043-3049. Erratum in: Eur Arch Otorhinolaryngol. 2019; 10. doi: 10.1007/s00405-019-05593-4.

52) Capaccio P, Ottaviani F, Cuccarini V, *et al*. Genetic and acquired prothrombotic risk factors and sudden hearing loss. Laryngoscope. 2007; 117 (3): 547-551. doi: 10.1097/MLG.0b013e31802f3c6a.

53) Ohlemiller KK, Gagnon PM. Cellular correlates of progressive hearing loss in 129S6/SvEv mice. J Comp Neurol. 2004; 469 (3): 377-390. doi: 10.1002/cne.11011.

54) Simões J, Vlaminck S, Seiça R, *et al*. Vascular mechanisms in acute unilateral peripheral vestibulopathy: a systematic review. Acta Otorhinolaryngol Ital. 2021; 41: 401-409. doi: 10.14639/0392-100X-N1543.

55) Simões J, Vlaminck S, Seiça R, *et al*. Cardiovascular Risk and Sudden Sensorineural Hearing Loss: A Systematic Review and Meta-Analysis. The Laryngoscope. 2023; 133: 15-24. doi: 10.1002/lary.30141.

56) Watson N, Ding B, Zhu X, *et al*. Chronic inflammation - inflammaging - in the ageing cochlea: A novel target for future presbycusis therapy. Ageing Res Rev. 2017; 40: 142-148. doi: 10.1016/j.arr.2017.10.002.

57) Rolim LP, Samelli AG, Moreira RR, *et al*. Effects of diabetes mellitus and systemic arterial hypertension on elderly patients' hearing. Braz J Otorhinolaryngol. 2018; 84 (6): 754-763. doi: 10.1016/j.bjorl.2017.08.014.

58) Bertrand RA, Huang Z. Association between audiometric patterns and probabilities of cardiovascular diseases. Laryngoscope Investig Otolaryngol. 2018; 3 (6): 478-485. doi: 10.1002/lio2.206.

59) Friedland DR, Cederberg C, Tarima S. Audiometric pattern as a predictor of cardiovascular status: Development of a model for assessment of risk. Laryngoscope 2009; 119: 473–486. doi: 10.1002/lary.20130.

60) Susmano A, Rosenbush SW. Hearing loss and ischemic heart disease. Am J Otol 1988; 9: 403–408.

61) Rubinstein M, Hildesheimer M, Zohar S, *et al*. Chronic cardiovascular pathology and hearing loss in the aged. Gerontology 1977; 23: 4–9. doi: 0.1159/000212167.

62) Agarwal S, Mishra A, Jagade M, *et al*. Effects of hypertension on hearing. Indian J Otolaryngol Head Neck Surg 2013; 65(Suppl 3): 614–618. doi: 10.1007/s12070-013-0630-1.

63) Rosenhall U, Sundh V. Age-related hearing loss and blood pressure. Noise Health 2006; 31: 88–94. doi: 10.4103/1463-1741.33539.

64) Talbott E, Findlay R, Kuller L, *et al*. Noise-induced hearing loss: A possible marker for high blood pressure in older noise exposed population. Journal of Occupational Medicine 1990: 690–697.

65) Hwang JH, Ho HC, Hsu MC, *et al*. Effect of transient ischemic attack on hearing thresholds of older subjects. Audiol Neurotol Extra 2011; 1: 1–8.

66) O'Neill M. Microvascularização arterial da cóclea. Tese para obtenção do grau de Doutor em Medicina na Especialidade em Cirurgia e Morfologia Normal na Faculdade de Ciências Médicas. 2015.

67) Morizane I, Hakuba N, Shimuzu Y, *et al*. Transient cochlear ischemia and its effects on the stria vascularis. Neuroreport 2005; 16: 799–802. doi: 10.1097/00001756-200505310-00004.

68) Lars-Göran J, Hawkins JE Jr. Symposium on basis ear research. II. Strial atrophy in clinical and experimental deafness. Laryngoscope 1972; 82: 1105–1125. doi: 10.1288/00005537-197207000-00002.

69) Schuknecht HF: Pathology of the Ear, ed 2, Philadelphia, 1993, Lea & Febiger.

70) Seidman MD, Khan MJ, Dolan DF, *et al*. Age-related differences in cochlear microcirculation and auditory brain stem response. Arch Otolaryngol Head Neck Surg. 1996; 122 (11): 1221-6. doi: 10.1001/archotol.1996.01890230067013.

71) Liew G, Wong TY, Mitchell P, *et al*. Retinal microvascular abnormalities and age-related hearing loss: the Blue Mountains hearing study. Ear Hear. 2007; 28 (3): 394-401. doi: 10.1097/AUD.0b013e3180479388.

72) Lee H, Kim JS, Chung EJ, *et al*. Infarction in the territory of anterior inferior cerebellar artery: spectrum of audiovestibular loss. Stroke 2009; 40: 3745-3751. doi: 10.1161/STROKEAHA.109.564682.

73) Amarenco P, Rosengart A, DeWitt LD. Anterior inferior cerebellar artery territory infarcts. Mechanisms and clinical features. Arch Neurol 1993; 50: 154-161. doi: 10.1001/archneur.1993.00540020032014.

74) Kumral E, Kisabay A, Ataç C. Lesion patterns and etiology of ischemia in the anterior inferior cerebellar artery territory involvement: a clinical - diffusion weighted - MRI study. Eur J Neurol 2006; 13: 395- 401. doi: 10.1111/j.1468-1331.2006.01255.x.

75) Amarenco P, Hauw JJ. Cerebellar infarction in the territory of the anterior and inferior cerebellar artery. A clinicopathological study of 20 cases. Brain 1990; 113: 139-155. doi: 10.1093/ brain/113.1.139.

76) Watanabe Y, Ohi H, Shojaku H, *et al*. Sudden deafness from vertebrobasilar artery disorder. Am J Otol 1994; 15: 423-426.

77) Wright JL, Saunders SH. Sudden deafness following cardio-pulmonary bypass surgery. J Laryngol Otol 1975; 89: 757-759. doi: 10.1017/s0022215100080956.

78) Raupp SF, Jellema K, Sluzewski M, *et al*. Sudden unilateral deafness due to a right vertebral artery dissection. Neurology 2004; 62: 1442. doi: 10.1212/01.wnl.0000120757.35082.35.

79) Liqun Z, Park KH, Kim HJ *et al*. Acute Unilateral Audiovestibulopathy due to Embolic Labyrinthine Infarction. Front Neurol 2018; 2 (9): 311. doi: 10.3389/fneur.2018.00311.

80) Oh EH, Rhee JK, Shin JH *et al*. Neutrophil-mediated immune response as a possible mechanism of acute unilateral vestibulopathy. J Vestib Res 2020; 30 (6): 363-374. doi : 10.3233/VES-200044.

81) Şahin Mİ, Kökoğlu K, Gülmez E. Mean platelet volume, neutrophil and platelet to lymphocyte ratios are elevated in vestibular neuritis. J Clin Neurosci 2019; 67: 134-138. doi: 10.1016/j. jocn.2019.05.062.

82) López-González MA, Abrante A, López-Lorente C, *et al*. Acute phase inflammatory response in idiopathic sudden deafness: patho- genic implications. Int J Otolaryngol 2012; 216592. doi: 10.1155/2012/216592.

83) Koçak HE, Elbistanlı MS, Acıpayam H, *et al*. Are neutrophil/lymphocyte and platelet/lymphocyte ratios related with formation of sudden hearing loss and its prognosis? Eur Ann Otorhinolaryngol Head Neck Dis 2017; 134: 383-386. doi: 10.1016/j.anorl.2016.06.005.

84) Seo YJ, Park YA, Bong JP, *et al*. Predictive value of neutrophil to lymphocyte ratio in first-time and recurrent idiopathic sudden sensori- neural hearing loss. Auris Nasus Larynx 2015; 42: 438-442. doi: 10.1016/j.anl.2015.04.011.

85) Beyan C, Beyan E. Mean platelet volume values may not be elevated in patients with vestibular neuritis. J Clin Neurosci 2019; 70: 269. doi: 10.1016/j.jocn.2019.08.052.

86) Navari E, Casani AP. Lesion patterns and possible implications for recovery in acute unilateral vestibulopathy. Otol Neurotol 2020; 41: e250-e255. doi: 10.1097/MAO.0000000000002476.

87) Oron Y, Shemesh S, Shushan S *et al*. Cardiovascular Risk Factors Among Patients with Vestibular Neuritis. Ann Otol Rhinol Laryngol 2017; 126 (8): 597-601. doi: 10.1177/0003489417718846.

88) Fishman JM. Corticosteroids effective in idiopathic facial nerve palsy (Bell's palsy) but not necessarily in idiopathic acute vestibular dysfunction (vestibular neuritis). Laryngoscope 2011; 121: 2494-2495. doi: 10.1002/lary.22327.

89) Halmagyi GM. Diagnosis and management of vertigo. Clin Med (Lond) 2005; 5: 159-165. doi: 10.7861/clinmedicine.5-2-159.

90) Uffer DS, Hegemann SC. About the pathophysiology of acute unilateral vestibular deficit - vestibular neuritis (VN) or peripheral vestibulopathy (PVP)? J Vestib Res 2016; 26 (3): 311-317. doi: 10.3233/VES-160581.

91) Mohammadi M, Taziki Balajelini MH, Rajabi A. Migraine and risk of sudden sensorineural hearing loss: a systematic review and meta-analysis. Laryngoscope Investig Otolaryngol. 2020; 5 (6): 1089-1095. doi: 10.1002/lio2.477.

92) Ullrich D, Aurbach G, Drobik C. A prospective study of hyperlipidemia as a pathogenic factor in sudden hearing loss. Eur Arch Otorhinolaryngol. 1992; 249: 273-276. doi: 10.1007/BF00714491.

93) Ballesteros F, Alobid I, Tassies D, *et al*. Is there an overlap between sudden neurosensorial hearing loss and cardiovascular risk factors? Audiol Neurootol. 2009; 14 (3): 139-145. doi: 10.1159/000171475.

94) Lin SW, Lin YS, Weng SF, *et al*. Risk of developing sudden sensorineural hearing loss in diabetic patients: a population-based cohort study. Otol Neurotol. 2012; 33 (9): 1482-1488. doi: 10.1097/MAO.0b013e318271397a.

95) Han W, Wang D, Wu Y, *et al*. Correlation between vestibular neuritis and cerebrovascular risk factors. Am j otolaryngol 2018; 39 (6): 751–753. doi: 10.1016/j.amjoto.2018.08.006.

96) Chung JH, Lee SH, Park CW, *et al*. Clinical Significance of Arterial Stiffness and Metabolic Syndrome Scores in Vestibular Neuritis. Otol Neurotol 2017; 38 (5): 737-741. doi: 10.1097/MAO.0000000000001352.

97) Wang S, Ye Q, Pan Y. Threshold effects between plasma total cholesterol level and the risk of sudden sensorineural hearing loss. Int J Clin Exp Med. 2019; 12 (10): 12441-12447.

98) Wang S, Ye Q, Pan Y. Serum non-high-density lipoprotein cholesterol is associated with the risk of sudden sensorineural hearing loss. Medicine (Baltimore). 2020; 99 (7): e19175. doi: 10.1097/MD.0000000000019175.

99) Chang SL, Hsieh CC, Tseng KS, *et al*. Hypercholesterolemia is correlated with an increased risk of idiopathic sudden sensorineural hearing loss: a historical prospective cohort study. Ear Hear. 2014; 35 (2): 256-261. doi: 10.1097/AUD.0b013e3182a76637.

100) Murofushi T, Tsubota M, Suzuki D. Idiopathic acute high-tone sensorineural hearing loss accompanied by vertigo: vestibulo-cochlear artery syndrome? Consideration based on VEMP and vHIT. J Neurol. 2019; 266 (8): 2066-2067. doi: 10.1007/s00415-019-09353-6.

101) Eliezer M, Toupet M, Guichard JP, *et al*. Cochleovestibular artery syndrome: consideration based on VHIT, VEMP, and inner ear MRI. J Neurol. 2019; 266 (9): 2327-2329. doi: 10.1007/s00415-019-09407-9.

102) Engdahl B, Aarhus L, Lie A, *et al*. Cardiovascular risk factors and hearing loss: The HUNT study. International Journal of Audiology. 2015; 54 (12): 958-66. doi: 10.3109/14992027.2015.1090631.

103) Horikawa C, Kodama S, Tanaka S, *et al*. Diabetes and risk of hearing impairment in adults: A meta-analysis. J Clin Endocrinol Metab. 2013; 98: 51–58. doi: 10.1210/jc.2012-2119.

104) Schuknecht HF. Further observations on the pathology of presbycusis. Arch Otolaryngo. 1964; 80: 369–382. doi: 10.1001/archotol.1964.00750040381003.

105) Gates GA, Cobb JL, D'agostino RB, *et al*. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. Arch Otolaryngol Head Neck Surg. 1993; 119: 156–161.doi: 10.1001/archotol.1993.01880140038006.

106) Gates GA, Schmid P, Kujawa SG, *et al*. Longitudinal threshold changes in older men with audiometric notches. Hear Res. 2000; 141(1-2): 220-8. doi: 10.1016/s0378-5955(99)00223-3

107) Lebech Cichosz S, Hejlesen O. Association between diabetes and changes in hearing: A cross-sectional study. Diabetes Metab. 2018; 44 (1): 87-90. doi: 10.1016/j.diabet.2017.02.002.

108) Friedman S, Schulman R, Weiss S. Hearing and diabetic neuropathy. Arch Intern Med. 1975; 135: 573–6.

109) Wattamwar K, Qian ZJ, Otter J, *et al*. Association of Cardiovascular Comorbidities With Hearing Loss in the Older Old. JAMA Otolaryngol Head Neck Surg. 20181; 144 (7): 623-629. doi: 10.1001/jamaoto.2018.0643.

110) Fisch U, Dobozi M, Greig D. Degenerative changes of the arterial vessels of the internal auditory meatus during the process of aging. A histological study. Acta Otolaryngol. 1972; 73 (2): 259-66. doi: 10.3109/00016487209138940.

111) Di Girolamo S, Quaranta N, Picciotti P, *et al*. Age-related histopathological changes of the stria vascularis: an experimental model. Audiology. 2001; 40 (6): 322–326.

112) Li HS, Borg E. Age-related loss of auditory sensitivity in two mouse genotypes. Acta Otolaryngol. 1991; 111 (5): 827-34. doi: 10.3109/00016489109138418.

113) Clinkard D, Amoodi H, Kandasamy T, *et al*. Changes in the cochlear vasculature and vascular endothelial growth factor and its receptors in the aging c57 mouse cochlea. ISRN Otolaryngol. 2013; 2013: 430625. doi: 10.1155/2013/430625.

Supplement Number 1

Protocol Approval: *Faculdade de Medicina da Universidade de Coimbra*

1 2 9 0 FACULDADE DE MEDICINA UNIVERSIDADE D COIMBRA

COMISSÃO DE ÉTICA DA FMUC

Of. Refª **126-CE-2019**
Data 16/12/**2019**

C/conhecimento ao aluno

Exmo. Senhor
Presidente do Conselho Científico da FMUC

Assunto: Projeto de Investigação no âmbito do Programa de Doutoramento em Ciências da Saúde (refª CE-126/2019)

Candidato(a): João Filipe Carvalho Pereira Mano Simões

Título do Projeto: *"Associação clínica entre perdas audio-vestibulares e eventos vasculares".*

A Comissão de Ética da Faculdade de Medicina, após análise do projeto de investigação supra identificado, decidiu emitir o parecer que a seguir se transcreve:

"Parecer favorável".

Queira aceitar os meus melhores cumprimentos.

O Presidente,

Prof. Doutor João Manuel Pedroso de Lima

HC

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Supplement Number 2

Protocol Approval: *Centre Hospitalier de Mouscron*

CENTRE HOSPITALIER DE MOUSCRON

Association sans but lucratif

Avenue de Fécamp, 49

7700. **Mouscron**

056 85 85 85

Comité d'Ethique n° d'agrégation OM 174

Mouscron le 30/06/2022

Au Docteur J. Simoes

CHM

Chère Conscœur, Cher Confrère,

Le Comité d'éthique a examiné votre demande d'étude rétrospective intitulée «CARDIOVASCULAR RISK FACTORS AMONG PATIENTS WITH ACUTE UNILATERAL INNER EAR HYPOFUNCTION: A CASE-CONTROL STUDY »

Investigateur local et Promoteur : Joao Simoes (service d'ORL, CHM)

Comité éthique central :

Le Comité d'éthique remet l'avis suivant :

S'agissant d'une étude rétrospective sur dossier, la législation belge ne nécessite pas de consentement éclairé. Cependant, si le patient a fait opposition à l'utilisation de ses données personnelles et médicales, ces dernières ne peuvent être utilisées.

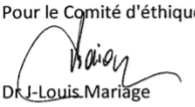
En aucun cas, des contacts ne pourront être pris avec les patients de cette étude sous peine de perdre le caractère rétrospectif et ainsi tomber dans le cadre de la loi sur l'expérimentation humaine qui exige un consentement éclairé du patient. Pour la même raison, aucun nouveau dossier à la date du début de l'étude ne pourra être collecté.

Avis favorable sur la faisabilité de l'investigation au Centre Hospitalier de Mouscron et sur la capacité du Docteur Simoes à conduire l'étude.

Le comité d'éthique rappelle cependant aux investigateurs et aux responsables de l'expérimentation qu'elle se réalisera sous leur responsabilité propre et que l'avis favorable donné par le Comité d'éthique ne signifie en rien qu'il en prend ou en partage la responsabilité.

Salutations confraternelles,

Pour le Comité d'éthique



Dr J-Louis Mariage

Président

Supplement Number 3

PROSPERO registration

NIHR | National Institute for Health Research

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Citation

João Simões, António Miguéis, Raquel Seiça, Stephan Vlaminck. Cardiovascular risk factors and sudden sensorineural hearing loss: A Systematic Review and Meta-Analysis. PROSPERO 2021 CRD42021274028 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021274028

Review question
Is there a relationship between cardiovascular risk factors and sudden sensorineural hearing loss?

Searches
PubMed (including MEDLINE)

EMBASE

Web of Science

Cochrane

Date: Inception - current

Only studies with humans

Types of study to be included
Studies quantitatively examining the relationships between exposures and outcomes:

- longitudinal, case-control, cross sectional

Condition or domain being studied
Sudden sensorineural hearing loss is defined as a decrease in hearing of ? 30 decibels affecting at least three consecutive frequencies within 72 hours or less. The estimated incidence is at least 5-20 per 100000/year and the spontaneous recovery rate is 32–65%. Epidemiological surveys suggest an increasing incidence of sudden deafness. Causal identification is found in only 10 to 30% of the cases without sufficient evidence. Several triggers have been proposed, including infectious, autoimmune, vascular, metabolic, hematological and neurological diseases.

Participants/population
Adults, aged 18 years and older.

Intervention(s), exposure(s)
Intervention/Exposures:

Objectively measured (using biochemical/ anthropometric measurements) or

self-reported/physician diagnosed cardiovascular risk factors (hypertension, diabetes, dyslipidemia)

Comparator(s)/control
Adults with no cardiovascular risk factors

Context

Main outcome(s)
Occurrence of sudden sensorineural hearing loss, objectively measured by pure tone audiometry (to determine hearing levels, a decrease in hearing of ? 30 decibels affecting at least three consecutive frequencies within 72 hours or less)

Measures of effect
OR's, HR's, RR's

Additional outcome(s)
None

Data extraction (selection and coding)
Inclusion Criteria:

- Studies assessing the relationship between cardiovascular risk factors and sudden sensorineural hearing loss in adults.

Exclusion Criteria:

- Non-human subjects

- Not published (preprint) or conference proceeding

- Case studies/series

- RCT's

- Studies related to safety, effectiveness of treatments for hearing loss

- Studies conducted in subgroups of patients (pregnant women, with stroke, specific health conditions etc..)

- Studies on other forms of hearing loss

Data to be extracted: author, year, country, sample, sampling method, age range, hearing loss assessment, effect size, confounding factors, conclusion.

A standardized form will be completed independently by 2 reviewers for data extraction.

Risk of bias (quality) assessment
Newcastle-Ottawa Scale (NOS)

Strategy for data synthesis
Qualitative synthesis of study results

Which factors are associated with sudden sensorineural hearing loss and to what degree?
The quantitative analysis of the data will be performed using descriptive statistics. Forest plots with pooled odds ratios (ORs) and hazard ratios (HRs) will be produced using Stata version 16 software (StataCorp, College Station, TX). Also, the heterogeneity among the studies will be assessed using the I^2 statistic. In the case of an I^2 statistic 50%, which indicates the existence of heterogeneity among studies, a random-effects model will be used; If I^2 statistic 50%, a fixed-effects model will be used. A two-sided P value 0.05 is set to be statistically significant.

Analysis of subgroups or subsets
Males versus Females

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Type and method of review
Epidemiologic, Meta-analysis, Systematic review

Anticipated or actual start date
15 July 2021

Anticipated completion date
31 October 2021

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None

Grant number(s)

State the funder, grant or award number and the date of award

None

Conflicts of interest

Language
English

Country
Belgium

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
17 September 2021

Date of first submission
17 August 2021

Stage of review at time of this submission

Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

17 September 2021
17 September 2021

Supplement Number 4

Online supplement of Cardiovascular risk and sudden sensorineural hearing loss: a systematic review and meta-analysis

Appendix 1. Literature search and in- and exclusion criteria

PICO search strategy:

Population: adult patients with idiopathic sudden sensorineural hearing loss (SSNHL)

Intervention: with or without known medical treatment

Comparison: individuals without SSNHL in cohort and case-control studies

Outcome: higher prevalence of cardiovascular risk factors

PUBMED

((((((((((((((((((sudden hearing loss) OR sudden deafness) OR sudden sensorineural hearing loss) OR SSNHL) OR SSHL) OR SSNHL) OR ISSHL) OR SHL) OR ISNHL) OR ISHL)))[MeSH Terms])))) OR ((((((((((((sudden hearing loss) OR sudden deafness) OR sudden sensorineural hearing loss) OR SSNHL) OR SSHL) OR SSNHL) OR ISSHL) OR SHL) OR ISNHL) OR ISHL)))))))) AND (vascular OR vascular disease OR cardiovascular* OR CVD OR cardiac)

((((((((((((((((sudden hearing loss) OR sudden deafness) OR sudden sensorineural hearing loss) OR SSNHL) OR SSHL) OR SSNHL) OR ISSHL) OR SHL) OR ISNHL) OR ISHL)))[MeSH Terms])))) OR ((((((((((((sudden hearing loss) OR sudden deafness) OR sudden sensorineural hearing loss) OR SSNHL) OR SSHL) OR SSNHL) OR ISSHL) OR SHL) OR ISNHL) OR ISHL))))))) AND ((risk factors) OR (diabetes) OR (lipids) OR (dyslipidemia) OR (hypertension))

EMBASE

('lipids' OR 'dyslipidemia' OR 'hypertension' OR 'diabetes' OR 'risk factor*') AND ('sudden hearing loss'/exp OR 'sudden hearing loss' OR 'sudden deafness'/exp OR 'sudden

deafness' OR 'sudden sensorineural hearing loss'/exp OR 'sudden sensorineural hearing loss' OR ssnhl OR sshl OR SSNHL
OR isshl OR shl OR isnhl OR ishl)

('vascular disease' OR 'cardiovascular disease') AND ('sudden hearing loss'/exp OR 'sudden hearing loss' OR 'sudden deafness'/exp OR 'sudden deafness' OR 'sudden sensorineural hearing loss'/exp OR 'sudden sensorineural hearing
loss' OR ssnhl OR sshl OR SSNHL OR isshl OR shl OR isnhl OR ishl)

WEB OF SCIENCE

(ALL=(sudden hearing loss) OR ALL=(sudden deafness) OR ALL=(sudden sensorineural hearing loss) OR ALL=(SSNHL) OR ALL=(SSHL) OR ALL=(SSNHL) OR ALL=(ISSHL) OR ALL=(SHL) OR ALL=(ISNHL) OR ALL=(ISHL)) AND (ALL=(cardiovascular*) or ALL=(CVD) or ALL=(vascular))

(ALL=(sudden hearing loss) OR ALL=(sudden deafness) OR ALL=(sudden sensorineural hearing loss) OR ALL=(SSNHL) OR ALL=(SSHL) OR ALL=(SSNHL) OR ALL=(ISSHL) OR ALL=(SHL) OR ALL=(ISNHL) OR ALL=(ISHL)) AND (ALL=(risk factors) OR ALL=(lipids) OR ALL=(diabetes) OR ALL=(dyslipidemia) OR ALL=(Hypertension))

COCHRANE

“risk factor” AND ((sudden hearing loss) OR (sudden deafness) OR (sudden sensorineural hearing loss) OR SSNHL OR SSHL OR SSNHL OR ISSHL OR SHL OR ISNHL OR ISHL)

"cardiovascular disease" AND ((sudden hearing loss) OR (sudden deafness) OR (sudden sensorineural hearing loss) OR SSNHL OR SSHL OR SSNHL OR ISSHL OR SHL OR ISNHL OR ISHL)

Exclusion criteria for title/abstract and full text screening:

Reviews/case reports/editorials/abstracts

Study abstracts/titles only

Animal studies

Not sudden sensorineural hearing loss

Outcome measure not Diabetes Mellitus, High Blood Pressure, Dyslipidemia or Metabolic Syndrome

Acute conductive hearing loss

Unclear presentation of data

Article not retrieved:

Preyer, S. *et al*. (1992). Prospective study of the cardiovascular risk of patients with sudden deafness. HNO 40(3): 79-85.

Supporting Table 1	
Summary of the results of the included studies	
Aimoni C, 2010[24]	DM, TC and a high burden of cardiovascular risk factors are associated with the risk of SSNHL
Cadoni G, 2010[25]	A statistically significant association was found between high TC serum levels and a high risk of SSNHL
Cadoni G, 2007[26]	High levels of TC remained significantly associated with a high risk of sudden sensorineural hearing loss
Fasano T, 2017[10]	Higher levels of blood glucose were found in SSNHL patients compared to controls
Chien CY, 2015[42]	The MetS patients have a 3.54-fold increased risk of acquiring SSNHL
Wang S, 2020[37]	Elevated serum non-HDL-C was strongly associated with increased risk of SSNHL
Jalali MM, 2020[29]	The rate of HDL-C, TG, and HBP was significantly higher in the SSNHL
Capaccio P, 2007[18]	The SSNHL patients had significantly higher levels of fibrinogenemia, cholesterolemia, and homocystinemia and lower levels of folatemia than the controls
Chang SL, 2014[27]	DM (adjusted HR = 1.44; 95% CI = 1.18–1.76) and HBP (adjusted HR = 1.23; 95% CI = 1.04–1.45) were independent risk factors for SSNHL
Ciccone MM, 2012[28]	The TC and LDL-C were significantly higher in the SSNHL patients than in the controls
Kaneva AM, 2019[30]	No significant differences between patients with SSNHL and control subjects in TC, TG and HDL-C levels were observed
Lee JS, 2015[31]	Elevated TC and TG levels, and increased BMI are significantly associated with the prevalence of SSNHL and its prognosis
Lin SW, 2012[40]	DM and CAD were significantly associated with an increased risk of developing SSNHL
Mohammed AA, 2014[32]	Significant difference between the means of lipid profile and blood sugar of the patients and the control group apart from HDL-c where there was no significant difference
Oreskovic Z, 2011[33]	Only higher cholesterol and LDL-c concentrations were found in patients with SSNHL
Rajati M, 2016[34]	Fasting blood sugar, lipid profile, and electrocardiogram revealed no significant difference between the two groups
Rinaldi M, 2020[35]	SSNHL patients presented a fasting glucose and blood pressure significantly higher compared to controls
Wang S, 2019[36]	The risk of developing ISSHL increased with increasing concentration of serum TC (only in the range between 139 mg/ dl and 280 mg/dl)
Weng T, 2013[38]	TC and LDL-c concentrations may be important factors in the pathogenesis of SSNHL
Marcucci R, 2005[39]	Hypercholesterolemia, may be associated with SSNHL, so indirectly supporting the hypothesis of a vascular occlusion in the pathogenesis of the disease
Rudack C, 2006[41]	Hypercholesterolemia and low HDL-c are apparently no major risk factors for SSNHL, whereas elevated fibrinogen levels and smoking are associated with an increased risk for SSNHL

Abbreviations: ATH index - atherogenic index; CAD - coronary artery disease; DM – diabetes mellitus; HBP – high blood pressure; HDL-c - high-density lipoprotein cholesterol; SSNHL – idiopathic sudden sensorineural hearing loss; LDL-c - low-density lipoprotein cholesterol; MetS - Metabolic syndrome; TC – total cholesterol; TG – triglycerides

Supporting Table 2

Detailed results of seven included studies in pooled analysis

Author, Year	SSNHL Patients	Controls	Risk Factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Aimoni C, 2010[24]	141	271	HBP	1.02 (0.64-1.60)	0.94 (0.58-1.53)
			TG (>140 mg/dL)	1.37 (0.80-2.36)	1.19 (0.67-2.11)
			DM	2.07 (1.04-4.10)	2.37 (1.15-4.86)
			TC (>201 mg/dL)	1.82 (1.07-3.10)	1.87 (1.07-3.26)
Cadoni G, 20010[25]	43	43	LDL-c	Not reported	0.74 (0.02-25.41)
Cadoni G, 2007[26]	30	60	LDL-c	Not reported	0.17 (0.01-1.98)
Jalali MM, 2020[29]	81	243	HBP	2.64 (1.11-6.29)	2.44 (0.97-6.14)
			TG (>150 mg/dL)	2.03 (1.15-3.58)	1.93 (1.06-3.48)
			DM	0.88 (0.47-1.66)	Not reported
Lee JS, 2015[31]	324	972	TG (>150 mg/dL)	Not reported	1.49 (1.076-2.080)
			LDL-c	Not reported	0.81 (0.534-1.232)
			TC (>200 mg/dL)	Not reported	2.20 (1.49-3.24)
Marcucci R, 2005[39]	155	155	TG (>98 mg/dL)	12.8 (6.4-27)	3.0 (0.3-42)
			HBP	0.7 (0.4-1.3)	0.4 (0.1-0.9)
			TC (>190 mg/dL)	19 (10-38.6)	19 (7-50.1)
Capaccio P, 2007	100	200	TC (>190 mg/dL)	Not reported	1.06 (1.04-1.08)

Abbreviations: CI - confidence interval; HBP – high blood pressure; SSNHL – idiopathic sudden sensorineural hearing loss; LDL-c - low-density lipoprotein cholesterol; OR - odds ratio; TC – total cholesterol; TG – triglycerides

Supporting Table 3

Summary of characteristics of studies analyzing MetS

First Author	Cases N Mean Age ±SD	Outcome	Measures in cases	Measures in controls	P
Jalali MM[29]	81 45.2±14.6	MetS, n (%)	12	27	>0.05
Chien CY[42]	181 48.7±14.1	MetS, n (%)	79 (43.7)	38 (19.3)	<0.01

Abbreviations: MetS - Metabolic syndrome; SD - Standard Deviation

Supporting Table 4

a) Detailed results of studies without adjusted analysis and insufficient number of studies to pool (< 2)

Author, Year	SSNHL Patients	Controls	Risk Factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Weng, T 2013[38]	250	250	TC	1.46 (1.21-1.76)	Not reported
			TG	0.98 (0.89-1.06)	Not reported
			HDL-c	0.85 (0.55-1.30)	Not reported
			LDL-c	1.63 (1.29-2.06)	Not reported
Wang S, 2020[37]	324	972	Non-HDL-c (mg/dL)	1.03 (1.02-1.03)	Q1 (<111) – Reference Q2 (112-127) – 4.34 (2.43-7.74) Q3 (128-158) – 7.08 (3.99-12.56) Q4 (159-341) – 20.88 (11.86-36.75)
Chien CY, 2015[42]	181	181	MetS	Not reported	3.54 (2.00-6.43)
Jalali MM, 2020[29]	81	243	MetS	1.46 (0.66-3.21)	Not reported
Rudack C, 2006[41]	142	84	TC	0.78 (0.43-1.40)	Not reported
			HDL-c	1.94 (1.07-3.51)	Not reported
			LDL-c	0.93 (0.52-1.68)	Not reported

b) Detailed results of cohort studies

Author, Year	SSNHL Patients	Controls	Risk Factor	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Lin SW, 2012[40]	26,556	26,556	DM	1.67 (1.36-2.04)	1.59 (1.29-1.96)
Chang SL, 2014[27]	73,957	73,957	Hypercholesterolemia	1.62 (1.40-1.86)	1.60 (1.39-1.85)

Abbreviations: CI – confidence interval; DM – diabetes mellitus; HR – hazard ratio; SSNHL – idiopathic sudden sensorioneural hearing loss; LDL-c – low-density lipoprotein cholesterol; MetS – metabolic syndrome; OR – odds ratio; Q-quartile; TC – total cholesterol; TG – triglycerides

Supporting Table 5
Risk of bias assessment (Modified Newcastle-Ottawa scale) – Cohort Studies

Cohort Studies	Selection				Comparability	Outcome			
Assessment Criteria/Study author	1. Representativeness of the exposed cohort	2. Selection of the non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest not present at start of study	5. Comparability of cohorts on the basis of the design or analysis	6. Assessment of outcome	7. Was follow-up long enough for outcomes to occur	8. Adequacy of follow up of cohorts	Overall Quality Assessment (Max = 9)
Chang SL, 2014[27]	*	*	*	*	**	*	*	*	9
Lin SW, 2012[40]	*	*	*	*	**	*	*	*	9

Supporting Table 6
Risk of bias assessment (Modified Newcastle-Ottawa scale) – Case-Control Studies

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Case-Control Studies	Selection				Comparability	Exposure			
Assessment Criteria/Study author	1. Is the case definition adequate?	2. Representativeness of the cases	3. Selection of controls	4. Definition of controls	5. Comparability of cases and controls on the basis of the design or analysis	6. Ascertainment of exposure	7. Same method of ascertainment for cases and controls	8. Non-response rate	Overall Quality Assessment (Max = 9)
Aimoni C, 2010[24]	*	*	*	*	**	*	*		8
Cadoni G, 2010[25]	*				*	*	*		4
Cadoni G, 2007[26]	*	*	*		*	*	*		6
Fasano T, 2017[10]	*	*	*		*	*	*	*	7
Chien CY, 2015[42]	*	*	*	*	**	*	*		8
Wang S, 2020[37]	*	*			*	*	*		5
Jalali MM, 2020[29]	*	*	*	*	**	*	*		8
Capaccio P, 2007[18]	*	*	*		*	*	*		6
Ciccone MM, 2012[28]	*					*	*		3
Kaneva AM, 2019[30]					*	*	*		3
Lee JS, 2015[31]	*	*	*	*	**	*	*	*	9
Mohammed AA, 2014[32]	*		*		*	*	*		5
Oreskovic Z, 2011[33]	*	*	*	*		*	*		6
Rajati M, 2016[34]	*	*	*			*	*		5
Rinaldi M, 2020[35]	*	*	*	*	**	*	*		8
Wang S, 2019[36]	*	*	*	*	**	*	*	*	9
Weng T, 2013[38]	*	*	*	*	**	*	*		8
Marcucci R, 2005[39]	*	*	*	*	**	*	*		8
Rudack C, 2006[41]	*	*	*	*	**	*	*	*	9

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Supplement Number 5

Thesis related Presentations

1. Surdez súbita e o risco de eventos vasculares agudos

João Simões, Clara Silva, Luis Cardoso, Ana Machado, Ana Amorim, João Ribeiro, Sofia Paiva, António Paiva

Associação Portuguesa de Otoneurologia

http://www.otoneuro.pt/index.php/artigos/artigos-para-discussao/217-surdez-subita-e-o-risco-de-eventos-vasculares-agudos

Introdução

A surdez súbita sensorioneuraI (SSSN) é definida como uma perda auditiva superior a 30 dB em três frequências contíguas e apresenta uma incidência estimada de 20/100000 habitantes (Stachler RJ *et al.*, 2012; Rudack *et al.*, 2006).

As etiologias potenciais são infecção por vírus, oclusão vascular, autoimunidade, tumores, entre outras. Apesar de muita investigação relativamente à sua etiologia, a maioria dos casos são idiopáticos e o debate acerca da sua fisiopatologia continua. A presença de factores de risco para doença vascular, a sua importância no desenvolvimento da surdez súbita e a ocorrência de doença vascular aguda após o episódio de SSSN têm sido alvo de particular atenção. A favor de uma causa vascular estão o início súbito e sintomas unilaterais na maioria dos casos (semelhança com enfarte agudo do miocárdio (EAM) e acidente vascular cerebral (AVC), as incidência e taxas de recuperação similares à oclusão da veia central da retina e a associação significativa com factores pro-trombóticos, como a hiperhomocisteinémia e mutação MTHFR C677T) (Massimo Fusconi *et al.*, 2012).

Nos trabalhos de Herng-Ching Lin *et al.*, conclui-se que a SSSN pode ser um sinal precoce de AVC e sugerem que os pacientes sejam submetidos a avaliação analítica e neurológica para identificar risco potencial de acidente vascular agudo num futuro próximo. Além disso, verificaram níveis plasmáticos significativamente aumentados de fibrinogénio e colesterol, quando comparados com a população em geral.

Assim, este trabalho tem como objectivo explorar a existência de factores de risco cardiovascular (CV) em doentes com SSSN e a ocorrência de eventos CV agudos após SSSN, comparando com grupo controlo, durante um período de follow-up de 4 a 9 anos.

Materiais e Métodos

Neste estudo de coorte retrospectiva analisaram-se 66 casos consecutivos de SSSN do serviço de Otorrinolaringologia do Centro Hospitalar e Universitário de Coimbra. O período de observação foi de 1 de Janeiro de 2007 a 31 de Dezembro de 2011, com um período de follow-up até 9 anos. A coorte de estudo incluiu os 66 doentes de SSSN e a coorte de controlo incluiu 66 doentes (escolhidos aleatoriamente) submetidos a septoplastia em 2007 no mesmo serviço. Foram considerados critérios de exclusão o diagnóstico prévio de SSSN, apneia obstrutiva do sono e antecedentes de AVC ou EAM. Como predictores de eventos CV foram estudados a SSSN, hipertensão arterial, dislipidémia e diabetes mellitus. O *outcome* avaliado foi a ocorrência de eventos CV agudos (EAM e AVC).

Todos os pacientes com SSSN foram submetidos a estudo analítico, audiograma tonal e impedanciometria, bem como estudo imagiológico, se justificado. A terapêutica da coorte de estudo foi de corticoterapia sistémica com ou sem corticoterapia intra-timpânica. A oxigenoterapia hiperbárica foi usada como terapêutica de recurso nos casos que não responderam à terapêutica de primeira linha.

A análise estatística foi realizada com software STATA®, versão 14, usando teste *Chi*-square, regressão logística múltipla e teste t-student. Efectuou-se, ainda, a análise de sobrevida com curvas Kaplan-Meier e long rank test. A significância estatística foi estabelecida a 0.05.

Resultados

A tabela 1 apresenta as características demográficas e co-morbilidades de interesse em ambos os grupos de estudo. Verifica-se que o grupo de SSSN apresenta um maior número de eventos cardiovasculares agudos (2 EAM e 7 AVC *vs* 2 AVC no grupo controlo), bem como uma maior prevalência de hipertensão arterial e dislipidémia, mas não de diabetes mellitus.

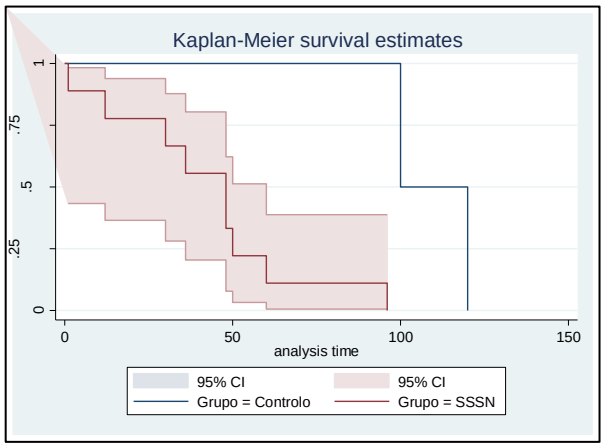
Tabela I. Características demográficas e co-morbilidades.

	Grupo SSSN (N=66)	**Grupo Controlo (N=66)**	***p-value***
Idade	52,8 (48,9 – 56,7)	51,7 (49,6 – 53,8)	> 0.05
Sexo Feminino	37	40	> 0.05
Sexo Masculino	30	27	

Evento Vascular Agudo	9	2	< 0.05
Hipertensão Arterial	19	9	< 0.05
Diabetes Mellitus tipo 2	5	3	> 0.05
Dislipidémia	22	11	< 0.05

Na análise multivariada verificou-se que doentes do grupo SSSN com hipertensão arterial e dislipidémia apresentaram um odds ratio para eventos CV agudos de 13,77 e 10,32, respectivamente (p<0.05). O predictor SSSN conferiu um odds ratio elevado (2,40), mas não estatisticamente significativo (p>0.05) para a ocorrência de eventos CV. Já na análise de sobrevida verificou-se que o grupo SSSN apresentou um maior número de eventos e mais precocemente do que o grupo controlo com significância estatística (p<0.05) (Fig.1).

Figura 1. Análise de sobrevida para eventos CV agudos.



Conclusões

Este trabalho evidencia a existência de um risco significativo de eventos CV agudos após surdez súbita quando comparado com grupo controlo, especialmente em doentes hipertensos e com dislipidémia. No entanto, verificam-se algumas limitações como a não consideração de obesidade, hábitos tabágicos, índice de massa corporal e variáveis sócio-económicas na análise multivariada (dados inconstantes nos registos). São considerados pontos fortes do estudo, o período alargado de follow-up (em comparação com estudos anteriores) e a análise multivariada.

A consideração da etiologia vascular em doentes de risco poderá permitir novas abordagens terapêuticas desta entidade, mas também eventuais medidas preventivas de eventos agudos e potencialmente fatais.

Referências:

- Herng-Ching Lin, Pin-Zhir Chao, Hsin-Chien Lee (2008) Sudden Sensorineural Hearing Loss Increases the Risk of Stroke. A 5-Year Follow-Up Study. Stroke. 39:2744-2748

- Massimo Fusconi, Antonio Chistolini, Armando de Virgilio, Antonio Greco, Fulvio Massaro, Rosaria Turchetta, Anna Teresa Benincasa, Mario Tombolini & Marco de Vincentiis (2012) Sudden sensorineural hearing loss: A vascular cause? Analysis of prothrombotic risk factors in head and neck, International Journal of Audiology. 51:11, 800-805

- Rudack C, Langer C, Stoll W (2006) Vascular risk factors in sudden hearing loss. Thromb Haemost. 95, 454–461

- Stachler RJ, Chandrasekhar SS, Archer SM (2012) Clinical practice guideline: Sudden hearing loss. Otolaryngol Head Neck Surg, 146, S1–35

2. Comorbidities in vestibular neuritis: is there a link with vascular events?

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Purpose of the study: Vestibular neuritis is a sudden loss of peripheral vestibular function, without cochlear and neurological findings. Seasonal variations in its incidence may indirectly support a viral etiology of vestibular neuritis. However, certain authors have also postulated that an ischemic process might be relevant for the etiology of this disease. Thus, the aim of this study is to analyze the comorbidities in vestibular neuritis, the seasonal variability and the occurrence of acute vascular events after the vertigo crisis.

Materials and methods: A retrospective cohort study of 231 patients admitted with the principal diagnosis of vestibular neuritis in a tertiary hospital between 2011 and 2013 was conducted with follow-up until 2016. For each subject the comorbidities and the occurrence of an acute vascular event were recorded. The demographic characteristics and comorbidities were analyzed using chi-square test. The survival study was carried out with Kaplan-Meier curves and long rank test was used for comparison. Multiple logistic regression was used to control for possible confounders. The seasonal variability of vestibular neuritis was tested with chi-square test and Rayleigh test.

Results: From the 231 vestibular neuritis patients, cardiovascular risk factors were present in 92 patients (40%) and 15 (6.5%) acute vascular events (stroke or acute myocardial infarction) were observed during the follow-up period. Patients with hypertension and hypercholesterolemia showed a significant association with acute vascular events ($p<0.001$), but when controlling for age there is no significant higher risk ($p>0.05$). In our cohort, significant seasonal variability was not observed.

Conclusions: Patients with vestibular neuritis present a high prevalence of cardiovascular risk factors with significant association with the occurrence of vascular events. Risk control should be mandatory for elderly vestibular neuritis patients. Although the viral etiology has been more often highlighted, the absence of seasonal variability in our cohort can support the importance of vascular etiology in vestibular neuritis.