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Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

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Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

Running title: ROSALIE study protocol

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The data will be published according to the STROBE-statement (Strengthening the Reporting of Observational studies in Epidemiology). The sponsor of this study (Gelre Hospital) will not interfere with public disclosure and publication of the research data.

Competing interest statement

The authors have no competing interest to declare in the study design or execution thereof.

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Abstract

Introduction: The etiology of sudden sensorineural hearing loss (SSNHL) is not certain in a significant number of cases. In 8-31% of posterior fossa infarctions acute hearing or vestibular loss precedes neurologic symptoms. Also, several retrospective cohort analyses have indicated a higher chance of experiencing a stroke after SSNHL compared to the general population. This higher incidence of stroke suggests vascular involvement in the pathophysiology of SSNHL. The aim of this study is to evaluate the association of cardiovascular disease and iSSNHL by investigating the presence of cardiovascular risk factors and cerebral small vessel disease, in patients with idiopathic SSNHL and compare this to controls

Method and analysis: In this multicentre cross-sectional study, 205 patients aged 50 years or higher diagnosed with idiopathic SSNHL, and 205 controls who are either suspected of trigeminus neuralgia, hemifacial spasm, vestibular paroxysmia, or have a cerebellopontine angle neoplasm, will be included. The primary outcome is the difference in cerebral small vessel disease, measured by the degree of white matter hyperintensities according to the Fazekas scale and the presence of brain infarctions on MRI, between patients with idiopathic SSNHL and controls. The secondary outcome is the difference in prevalence of the cardiovascular risk factors: hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction between both cohorts.

Ethics and dissemination: Patients will receive the standard diagnostic protocol for iSSNHL in the Netherlands; which consists of pure tone audiometric assessment before and after treatment with

corticosteroids and an MRI of the cerebellopontine angle displaying the entire cerebrum. Data will not be available publicly but might be shared upon reasonable request.

Registration:

The Medical Research Involving Human Subjects Act does not apply to this study, as has been declared by the regional review board at Leiden University Hospital, registration number 22-3060.

Keywords:

Sudden deafness, MRI, white matter hyperintensities

Strengths and limitations

Strengths:

- Multicenter study using hospital derived data
- Radiological assessment by two expert radiologists

Limitations:

- MRI sequences might slightly differ between participating centers
- Not all patients with iSSNHL will receive an MRI. In some patients hearing has recovered by the time the MRI scan is scheduled and at that point imaging is redundant.

Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency. It is commonly defined as a rapid-onset sensorineural hearing loss of more than 30dB in at least 3 contiguous audiometric frequencies occurring within 72 hours[1–3].

The incidence of SSNHL is approximately 5-20 per 100.000 persons per year. In 32-72% of the cases the hearing loss recovers spontaneously [4,5]. Unfortunately, in 30-50% percent of cases, hearing loss does not improve after therapy with high-dose corticosteroids, which is the generally accepted treatment modality in the Netherlands, based on the assumption of an infectious etiology [6].

In most cases the etiologic factor cannot be identified. One of the current hypotheses comprises vascular involvement in the pathophysiology of SSNHL. Since the internal auditory artery (IAA) is an end artery with little collateral blood supply, the cochlea is particularly vulnerable to ischemia [7,8]. Research has focused on associations between idiopathic SSNHL (iSSNHL) and systemic cardiovascular disease to investigate the plausibility of vascular involvement in the pathophysiology of SSNHL. The cardiovascular risk factors smoking, alcohol abuse and hypercholesterolemia were present more frequently in patients with SSNHL than in controls. Also, several large cohort studies in Taiwan and Korea found increased incidences of stroke following iSSNHL compared to the general population[9–1213]. In a meta-analysis performed by Lammers et al., the hazard risk of developing stroke after experiencing SSNHL was 1.42[14]. Kim et al. identified that in 8-31% of patients with a CVA in the posterior circulation, the neurologic symptoms were preceded by hearing loss or vestibular loss within a month before onset[15]. Sudden hearing loss might therefore be an indicator of stroke and warrant interventions to prevent cardiovascular events that are known to have significant morbidity and mortality.

Though the exact pathophysiology of cerebral small vessel disease (CSVD) is not clarified, it is expected to result fromsystemic cardiovascular disease, especially hypertension[16]. The presence of

CSVD raises the chance of developing stroke and other vascular neurodegenerative diseases like vascular dementia[17–19]. We hypothesize that patients with iSSNHL will have more cerebral small vessel disease compared to the general population, due to the increased cardiovascular comorbidity. CSVD can be visualized on MRI by the presence of white matter hyperintensities (WMH), cerebral microbleeds, lacunes and silent brain infarctions[18].

With this multicenter cross-sectional analysis based on hospital derived data, we will investigate the presence of WMH and brain infarctions on MRI in elderly patients with iSSNHL and compare this to a control cohort. Also, we will compare the prevalence of cardiovascular risk factors between both cohorts.

Method and analysis

Design

Patients will be included within 2 years at participating hospitals in both the Netherlands and Belgium. We opt for collaboration with a minimum of 8 participating hospitals. So far the included centres of participation are Gelre Hospital Zutphen and Apeldoorn, Leiden University Medical Centre and the University Hospital of Antwerp. A total of 410 patients will be included, 205 patients in the study cohort and 205 subjects without iSSNHL in the control cohort. Patients will be recruited in the participating centres, though all data will be gathered and analysed at the Apeldoorn Dizziness Centre (ADC).

The ADC is located in Gelre Hospital location Apeldoorn. It serves as a multidisciplinary tertiary referral centre involving the Neurology, Otorhinolaryngology and Clinical Neurophysiology departments and specialises in the diagnostic and therapeutic workup of Dizziness. The ADC will serve as the coordinating centre for this study.

Inclusion

Patients recruited for the study cohort will be Dutch and Belgian residents diagnosed with iSSNHL, living in the service area of participating hospitals. The inclusion and exclusion criteria can be found in table 1.

The control cohort will be compiled of patients who present at the ADC or Gelre hospital with a suspected diagnosis of trigeminal neuralgia, hemifacial spasm or vestibular paroxysmia and patients with a cerebellopontine neoplasm who received a tertiary referral to and are treated at the Leiden University Medical Centre or University Hospital of Antwerp.

Sample size calculation

A sample size calculation was performed using nQuery software (Statsols, San Diego, CA, USA). Since the main outcome variable, the Fazekas score, is an ordinal variable, the sample size was calculated using a Mann-Whitney U rank-sum test with a 0.05 two-sided significance level. For the sample size calculation, we used the proportions of patients in each Fazekas score category as was previously observed in our retrospective case-controlled study comparing cerebral small vessel disease in patients with vestibular neuritis (VN) and a control cohort[20]. The control population in this previous study is comparable with literature that describes a Fazekas score of 2 to be expected in patients that are 60-70 years old[21]. Since we hypothesize there to be more cardiovascular comorbidity in patients with SSNHL compared to the general population, we expect the median Fazekas score in the SSNHL patients to be 3.

Figure 1 displays the output of the sample size calculation, indicating that inclusion of 205 patients in each of the two groups (i.e., SSNHL and controls) yields 80.72% power to reject the null hypothesis (i.e. equal distribution of proportions of patients over the 7 Fazekas score categories in the SSHNL

group and the control groups, the latter derived from our previous study[20] and shown in the bottom part of Figure 1).

Study outcomes

The primary outcome is the difference in cerebral small vessel disease on MRI between patients with iSSNHL and controls. This is evaluated by the degree of white matter hyperintensities using the Fazekas score and the presence of brain infarctions. The Fazekas score is the most frequently used diagnostic tool to assess the severity of white matter hyper-intensities in the periventricular with matter and the deep white matter[19,22]. It is an ordinal scale with a possible score from 0 to 6, see figure 2. Brain infarctions were defined as lesions of the brain with a minimal diameter of 3mm, a cerebrospinal fluid appearance in grey intensity on FLAIR or T2 MRI sequences and clearly differentiable from leukoaraiosis and dilated Virchow-Robinson spaces[23]

The secondary outcome is the prevalence of the cardiovascular risk factors age, gender, hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction. Hypertension will be defined by the following criteria: a. having a medical history of physician diagnosed hypertension and/or b. taking antihypertensive drugs. Hypercholesterolemia will be defined by the following criteria: a. having a medical history of physician diagnosed hypercholesterolemia and/or b. the use of lipid-lowering medication. BMI will be measured by the patients weight in kilogram divided by their height in squared meters at the time of iSSNHL diagnosis. Smoking status will be recorded as former and current and non-smoker. Diabetes will be defined by the following criteria: a. having a medical history of physician diagnosed diabetes mellitus and/or b. the use of oral hypoglycemic drugs or insulin. Finally, binary and multinomial logistic regression analysis will be used to compare the

primary and secondary outcomes between the cohorts while taking into account possible confounders such as treatment modality, in case theMRI is performedafter therapy.

Treatment modalities

Corticosteroid therapy

The usual treatment for patients with iSSNHL is an oral corticosteroid regimen of 1mg/kg/day of prednisolone with a maximum of 60mg a day for a duration of 7 up to 14 days, thereafter reduced until 0 within the same timeframe[24]. In case of a contraindication for oral corticosteroid use, intratympanic corticosteroid therapy is recommended. A 0.4ml - 0.8ml injection with dexamethasone, 10mg/ml, or methylprednisolone, 30 to 40mg/ml, will be injected into the middle ear every 3 to 7 days, in a maximum of 4 sessions. In case no adequate hearing improvement occurs after oral corticosteroid therapy, intratympanic corticosteroid injection can be considered for salvage therapy.

Hyperbaric oxygen therapy

In Belgium hyperbaric oxygen therapy (HBOT) is commonly used as treatment modality for sudden sensorineural hearing loss. Hyperbaric oxygen therapy can either be combined with oral corticosteroids as treatment strategy or used as a salvage therapy after corticosteroid therapy has not resulted in improved hearing. Hyperbaric oxygen will be administered by facemask in a pressurized room at around 2.5 atmosphere, in a session of 90 up to 120 minutes. This session will be repeated 10 times[25,26].

In the Netherlands HBOT is not part of the regular therapeutic workup due to the limited evidence and high costs[27].

Study procedures:

Subject identification and inclusion

Patients eligible for the study cohort will be recruited by their own ENT-surgeon at the participating centres in both The Netherlands and Belgium. Patients eligible for the control cohort will be recruited by neurologists or ENT-surgeons in Gelre Hospital and ENT-surgeons in Leiden University Medical Center and University Hospital Antwerp.

Data collection

Informed consent will be obtained during a telephone interview several days after a patient received the written patient information. During this telephone interview the patient will sign the informed consent form and return this through postal mail to the research team at Gelre Hospital. After the informed consent form has been signed the patient's symptoms at onset of iSSNHL will be identified and the medical history and medication use verified with a questionnaire during the same telephone interview.

When the signed informed consent form is received by the co-ordinating investigator, all relevant data acquired in the participating hospital will be sought from the participating hospitals. This data include: age, weight, height, the patient's medical history, current medication use and their latest MRI scan. The MRI scans of University Hospital Antwerp will not be shared due to international data transfer restrictions. For the SSNHL cohort results from pure tone audiometric tests before and after corticosteroid therapy, video-head impulse test results and/or calorimetric test results, if performed, and details regarding the received treatment strategy will also be gathered.

MRI assessment

MRI's will be included in the study if they have been performed within half a year prior to the sudden deafness, or within 3 months afterwards. In order to be adequately analysed, the MRI needs to have either a T2 or FLAIR sequence of the entire brain. An MRI of the cerebellopontine angle or entire brain is part of regular diagnostic work-up, though the scanning protocol might differ somewhat between the participating centres. Likewise, not all patients will be eligible for inclusion, since sometimes the scanning protocol only includes depiction of the cerebellopontine angle. The MRI scans retrieved in the Netherlands will be assessed by 2 neuroradiologist separately. Both radiologists have multiple years of experience in MRI assessment of head and neck pathology. The MRI scans of patients included in Antwerp will be assessed by the neuroradiologist of the University Hospital Antwerp. Figure 2 shows the scoring sheet for the MRI assessment. If the degree of white matter hyperintensities differs 2 or more points on the Fazekas scale, the radiologist will assess the MRI together until consensus is reached. Previous MRI assessment performed by both radiologists involved in this study demonstrated a substantial interrater agreement for white matter hyperintensity assessment using the Fazekas score, with a kappa of 0.74[20].

Ethics and dissemination

Informed consent

Informed consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and a minimal of 5 days reflection time has passed. The right of the participant to refuse to participate without giving reasons will be respected. If patients do not give consent in participating in the study, their contact information will thereafter be deleted.

Data handling

Personal data including medical history and diagnostic test results from will be sent to the investigating site by digitally protected email, after informed consent has been obtained.

Upon arrival in the Gelre Hospital, the relevant data will be extracted from the received files, pseudonomised and stored in a research database using Castor EDC (Castor EDC, Amsterdam, The Netherlands). The files themselves will be stored on a protected data drive of the ADC.

MRI scans from hospitals in the Netherlands will be shared electronically using the national Twiin platform for data exchange developed by VZVZ. (Vereniging van Zorgaanbieders voor Zorgcommunicatie, Den Haag, The Netherlands). The MRI scans will be pseudonymised and uploaded to a secured picture archiving and communication system (PACS) worklist at the radiology department of the Gelre Hospital Apeldoorn. After assessment of the pseudonymised MRI-scans, this PACS worklist will be deleted after the MRI scans have been stored on a protected data drive of the ADC.

MRI scans from Antwerp will be assessed by their own neuroradiologists, due to data international transfer restrictions.

The assembled document files, digital files and MRI-scans will be saved for 15 years on a protected data drive of the ADC. When this period has passed, all data will be deleted and all files destroyed.

Risks and benefits

The MRI scan and audiometric testing are standard medical practice when SSNHL is suspected; patients will not receive additional study related interventions. We will not include any blood

investigation or other procedure outside the SSNHL treatment guideline in the Netherlands and Belgium.

Implications for future research

The identification of vascular involvement in the onset of sudden deafness could have serious consequences for the current guideline for treatment of sudden hearing loss. In a subset of patients that appears to have increased cardiovascular comorbidity, cardiovascular risk management with anticoagulant administration could be considered. If the results of the cross-sectional study, as described in this paper, demonstrate evidence for vascular involvement in the pathophysiology of sudden sensorineural hearing loss, follow-up of the included study population can be considered. This follow-up could entail a retrospective investigation of the incidence of stroke in the five years after inclusion in this study.

Data deposition

Upon reasonable request the data and statistical code could be shared. The dataset will not be publicly accessible. The protocol will be published open access to stimulate transparency and improve future research.

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Tables

Inclusion criteria sudden deafness cohort	*Inclusion criteria control cohort*
• Sudden deafness defined by acute onset sensorineural hearing loss of at least 30dB on 3 consecutive frequencies occurring withing 72 hours or less. • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years	• Patients diagnosed with trigeminal neuralgia, hemifacial spasm, vestibular paroxysmia or a cerebellopontine neoplasm. • Absence of sudden sensorineural hearing loss • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years
Exclusion criteria	
• Diagnosis of sudden deafness prior to the study period. • Significant cerebral damage due to a pre-existing medical condition that will impede an adequate assessment of the degree of cerebral small vessel disease. For instance, a medical history of multiple sclerosis. • Presence of an enlarged vestibular aqueduct on MRI that could be responsible for SSNHL • An identifiable cause of ıSSNHL such as a Borrelia Burgdorferi infection.	

Table 1. Inclusion and exclusion criteria for participation in the ROSALIE study. FLAIR=fluid attenuated inversion recovery, iSSNHL=idiopathic sudden sensorineural hearing loss.

Figure legends

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

Figure 2. MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

Authors contributions

All authors have contributed to the study design. F. Oussoren and T.D. Bruintjes are responsible for the overall conduct of the study. C. Colijn and F. Oussoren will be responsible for the data collection. F. Oussoren and T. Schermer will be responsible for the statistical analysis. J. Kardux and L. Poulsen will be responsible for the MRI assessment. E. Hensen and M. Lammers will be responsible for the of the control cohort

MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test for Ordered Categories

	1		
Test Significance Level, a	0.050		
1 or 2 Sided Test?	2		
Number of Categories, k	7		
Side Table Name	MTT2S-1		
p1 P(X<Y)			
Power (%)	80.72		
Sample Size per Group, n	205		

MTT2S-1

Σ Compute ↕ Transfer X Clear

Category	Proportion in Controls (X)	Proportion in SSNHL (Y)
1	0.079	0.070
2	0.296	0.191
3	0.300	0.264
4	0.192	0.307
5	0.079	0.103
6	0.039	0.041
7	0.015	0.024
Σπi	1.000	1.000
p1 = P(X<Y)	0.578	

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

134x129mm (96 x 96 DPI)

1. Fazekas score

A. periventricular white matter (PVWM)	
	0 = absent
	1 = "caps" or pencil-thin lining
	2 = smooth "halo"
	3 = irregular periventricular signal extending into the deep white matter
B. deep white matter (DWM)	
	0 = absent
	1 = punctate foci
	2 = beginning confluence
	3 = large confluent areas
	Total: 0 up to 6.

2. (Silent) brain infarctions*

	Yes= 1 / No= 0	Remarks
Presence		
Size (in mm)		

*SBI's need to meet the following criteria:
1. Minimal size of 3mm
2. Cerebrospinal fluid (CSF) appearance in all MRI sequences.
3. Can be differentiated from dilated Virchow-Robin spaces (dVRS)

MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

127x132mm (96 x 96 DPI)

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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Head & neck imaging < RADIOLOGY & IMAGING, OTOLARYNGOLOGY, Audiology < OTOLARYNGOLOGY

Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

Running title: ROSALIE study protocol

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Abstract

Introduction: The etiology of sudden sensorineural hearing loss (SSNHL) is not certain in a significant number of cases. In 8-31% of posterior fossa infarctions acute hearing or vestibular loss precedes neurologic symptoms. Also, several retrospective cohort analyses have indicated a higher chance of experiencing a stroke after SSNHL compared to the general population. This higher incidence of stroke suggests vascular involvement in the pathophysiology of SSNHL. The aim of this study is to evaluate the association of cardiovascular disease and iSSNHL by investigating the presence of cardiovascular risk factors and cerebral small vessel disease, in patients with idiopathic SSNHL and compare this to controls

Method and analysis: In this multicentre cross-sectional study, 205 patients aged 50 years or higher diagnosed with idiopathic SSNHL, and 205 controls who are either suspected of trigeminus neuralgia, hemifacial spasm, vestibular paroxysmia, or have a cerebellopontine angle neoplasm, will be included. The primary outcome is the difference in cerebral small vessel disease, measured by the degree of white matter hyperintensities according to the Fazekas scale and the presence of brain infarctions on MRI, between patients with idiopathic SSNHL and controls. The secondary outcome is the difference in prevalence of the cardiovascular risk factors: hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction between both cohorts.

Ethics and dissemination: Patients will receive the standard diagnostic protocol for iSSNHL in the Netherlands; which consists of pure tone audiometric assessment before and after treatment with corticosteroids and an MRI of the cerebellopontine angle displaying the entire cerebrum. Data will not be available publicly but might be shared upon reasonable request.

Registration:

The Medical Research Involving Human Subjects Act does not apply to this study, as has been declared by the regional review board at Leiden University Hospital, registration number 22-3060.

Keywords:

Sudden deafness, MRI, white matter hyperintensities

Strengths and limitations

Strengths:

- Multicenter study using hospital derived data
- Radiological assessment by two expert neuroradiologists

Limitations:

- MRI sequences might slightly differ between participating centers
- In patients whose hearing has recovered by the time the MRI scan is scheduled will not be included in the study
- MRI Assessment in Antwerp is performed by separate neuroradiologists

Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency, commonly defined as the abrupt onset of sensorineural hearing loss exceeding 30dB in at least 3 contiguous audiometric frequencies, manifesting within a span of 72 hours[1], [2], [3].

The annual incidence of SSNHL is approximately 5-20 cases per 100.000 individuals. In 32-72% of the cases the hearing loss recovers spontaneously [4],[5]. Unfortunately, in 30-50% percent of cases, hearing loss does not improve after treatment with high-dose corticosteroids, which is the generally accepted treatment modality in the Netherlands, based on the suspicion of an inflammatory etiology [6].

While the etiologic factor in most cases cannot be identified, one hypothesis under examination implicates vascular involvement in the pathophysiology of SSNHL. Given that the internal auditory artery (IAA) is an end artery with little collateral blood supply, the cochlea is particularly susceptible to ischemia [7], [8]. Research has focused on the potential link between idiopathic SSNHL (iSSNHL) and systemic cardiovascular disease, aiming to investigate the plausibility of vascular involvement in the pathophysiology of SSNHL. Multiple studies have reported higher prevalences of cardiovascular risk factors, such as smoking, alcohol abuse and hypercholesterolemia, in patients with SSNHL compared to controls[9], [10], [11], [12], [13].

Additionally, several cohort studies in Taiwan and Korea have reported increased incidence of stroke following iSSNHL[14], [15], [16], [17][18]. In a meta-analysis, Lammers et al. calculated the hazard risk of developing stroke after experiencing SSNHL to be 1.42[19]. Kim et al. reported that in 8-31% of patients experiencing posterior circulation cerebrovascular accidents (CVA) exhibited preceding hearing or vestibular loss within a month[20]. Sudden hearing loss might therefore be an indicator of stroke and warrant interventions to prevent cardiovascular events, known for their significant morbidity and mortality.

While the exact pathophysiology of cerebral small vessel disease (CSVD) is not clarified, it is widely believed to result from systemic cardiovascular disease, particularly hypertension[21]. The presence of CSVD elevates the risk of stroke and other vascular neurodegenerative conditions, including vascular dementia[22], [23], [24]. We hypothesize that patients with iSSNHL will exhibit a higher prevalence of cerebral small vessel disease than healthy individuals, due to their increased cardiovascular comorbidity. CSVD can be visualized on MRI by the presence of white matter hyperintensities (WMH), cerebral microbleeds, lacunes and silent brain infarctions[23].

To investigate this hypothesis, we will conduct a multicenter cross-sectional analysis based on hospital derived data. Our study aims to investigate the presence of WMH and brain infarctions on MRI in elderly patients with iSSNHL, comparing these findings with a carefully matched control cohort. Additionally, we will compare the prevalence of cardiovascular risk factors and comorbidity between both cohorts.

Method and analysis

Design

Patients will be included within a two-year period starting from may 2023 at participating hospitals in both the Netherlands and Belgium. The participating centres are Gelre Hospital Apeldoorn and Zutphen, Leiden University Medical Centre, Groene Hart hospital Gouda, Rijnstate hospital Arnhem, Treant Emmen, Saint Franciscus Gasthuis Rotterdam, Medisch spectrum Twente, Isala Zwolle, Rivierenland Tiel and the University Hospital of Antwerp. A total of 410 patients will be included, 205 patients with idiopathic SSNHL and 205 subjects without iSSNHL in the control cohort. Patients will be recruited in the participating centres, but all data collection and subsequent analysis will be centralized and conducted at the Apeldoorn Dizziness Centre (ADC).

The ADC, located within the Gelre Hospital location Apeldoorn, serves as a multidisciplinary tertiary referral centre involving the Neurology, Otorhinolaryngology and Clinical Neurophysiology departments. The ADC specialises in the diagnostic and therapeutic workup of Dizziness.

Inclusion

The study cohort will comprise patients diagnosed with iSSNHL and reside within the service areas of participating hospitals. A detailed description of the inclusion and exclusion criteria can be found in table 1.

The control cohort will consist of patients presenting at the ADC or Gelre hospital with suspected diagnoses of trigeminal neuralgia, hemifacial spasm or vestibular paroxysmia, as well as patients with cerebellopontine neoplasms who have been referred to and are treated at the Leiden University Medical Centre or University Hospital of Antwerp.

Patients with a preexisting medical condition that could cause significant cerebral damage, for instance multiple sclerosis or systemic vasculitis and could consequently interfere with the MRI assessment of white matter hyperintensities will be excluded from participation.

Sample size calculation

A sample size calculation was conducted using nQuery software (Statsols, San Diego, CA, USA). Since the main outcome variable, the Fazekas score, is an ordinal variable, the sample size was calculated using a Mann-Whitney U rank-sum test with a two-sided significance level of 0.05. To perform this calculation, we used the proportions of patients falling into each Fazekas score category, as was previously observed in our retrospective case-control study comparing cerebral small vessel disease in patients with vestibular neuritis (VN) and a control cohort[25]. The control population in this previous study aligns with literature, where a Fazekas score of 2 is expected in individuals aged 60-70 years[26]. Given our hypothesis of greater cardiovascular comorbidity in patients with SSNHL

compared to the general population, we expect the median Fazekas score in the SSNHL patients to be 3.

Figure 1 displays the output of the sample size calculation, demonstrating that the inclusion of 205 patients in each of the two groups (i.e., SSNHL and controls) yields 80.72% power to reject the null hypothesis. This null hypothesis posits that the distribution of patients across the 7 Fazekas categories in the SSNHL cohort and the control cohort is equal (i.e. the latter is derived from our previous study[25] and shown in the bottom part of Figure 1).

Study outcomes

The primary objective of this study is to assess the difference in prevalence of cerebral small vessel disease on MRI between patients diagnosed with iSSNHL and controls. This evaluation is based on two parameters, the extent of white matter hyperintensities, quantified on FLAIR/T2 weigthed images using the Fazekas score and the presence of brain infarctions. The Fazekas score is the most frequently used diagnostic tool to assess the severity of white matter hyperintensities in both periventricular and deep white matter regions[24], [27]. It is an ordinal scale ranging from 0 to 6, see figure 2. Brain infarctions were defined as lesions of the brain with a minimal diameter of 3mm, in the acute phase brain infactions demonstrate restricted diffusion, a cerebrospinal fluid like intensity on FLAIR or or T2 MRI sequences and clearly differentiable from leukoaraiosis and dilated Virchow-Robinson spaces[28]

The secondary outcome is the prevalence of the cardiovascular risk factors age, gender, hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction. Hypertension is defined by meeting either of the following criteria: a. having a medical history of physician diagnosed hypertension and/or b. taking antihypertensive drugs. Hypercholesterolemia is defined by meeting either of these criteria: a.

having a medical history of physician diagnosed hypercholesterolemia and/or b. the use of lipid-lowering medication. BMI is calculated by dividing the patients' weight in kilogram by the square of their height in meters at the time of iSSNHL diagnosis. Smoking status is recorded as either former, current or non-smoker. Diabetes is defined by either having a medical history of physician diagnosed diabetes mellitus and/or the use of oral hypoglycemic drugs or insulin.

Aditionally, to account for potential confounding factors, binary and multinomial logistic regression analyses will be performed to compare the primary and secondary outcomes between both cohorts.

Treatment modalities

Corticosteroid therapy

The standard treatment for patients with iSSNHL is an oral corticosteroid regimen, consisting of 1mg/kg/day of prednisolone with a maximum of 60mg, administered for a period of 7 up to 14 days, Subsequently, the dosage is gradually reduced to zero over the same timeframe[29]. In case of a contraindication for oral corticosteroid use, intratympanic corticosteroid therapy is recommended. A 0.4ml to 0.8ml injection of either dexamethasone (10mg/ml) or methylprednisolone (30 to 40mg/ml) is injected into the middle ear every 3 to 7 days, for a maximum of 4 sessions. If no significant improvement in hearing is observed following oral corticosteroid therapy, intratympanic corticosteroid injection can be considered for salvage therapy.

Hyperbaric oxygen therapy

In Belgium, hyperbaric oxygen therapy (HBOT) is commonly used as treatment option for sudden sensorineural hearing loss. Hyperbaric oxygen therapy can either be combined with oral corticosteroids or used as a salvage therapy when corticosteroid therapy fails to resulted in hearing recovery. The procedure involves administering hyperbaric oxygen via a facemask in a pressurized

chamber at around 2.5 atmospheres, with each session lasting 90 up to 120 minutes. This session will be repeated 10 times[30], [31].

It is important to note that In the Netherlands HBOT is not part of the regular therapeutic workup due to the limited supporting evidence and high costs[32].

Study procedures:

Subject identification and inclusion

Patients eligible for the study cohort will be recruited by their respective Ear, Nose and Throat (ENT) surgeons at participating centres in both The Netherlands and Belgium. Patients eligible for the control cohort will be recruited by neurologists or ENT-surgeons at Gelre Hospital and ENT-surgeons in Leiden University Medical Center and University Hospital Antwerp.

Data collection

Informed consent will be obtained during a telephone interview conducted several days after the patient receives the written patient information about the study. During this telephone interview, the patient will sign the informed consent form and return it to the research team at Gelre Hospitals, through postal mail. The interview will also include the identification of the patient's symptoms at the onset of iSSNHL, verification of their medical history and medication use.

Once the signed informed consent form is received by the coordinating investigator, relevant data from the participating hospitals will be sought. This data includes the patient's age, weight, height, medical history, current medication uses and their most recent MRI scan. MRI scans from University Hospital Antwerp will not be shared due to international data transfer restrictions. For the SSNHL cohort, results from pure tone audiometric tests conducted before and after corticosteroid therapy,

as well as results from video-head impulse testing and/or calorimetric tests, if performed, will be gathered. Additionally, details regarding the received treatment strategy will be collected.

MRI assessment

MRI scans will be included in the study if they were performed within six months prior to the onsef of sudden deafness or within 3 months afterwards. In order to be adequately analysed, the MRI requires either a T2 or FLAIR sequence of the entire brain. Susceptibility weighted images are relevant to demonstrate microbleeds. Diffusion weighted images are essential to demonstrate acute lesions. While an MRI of the cerebellopontine angle or entire brain with contrast is part of regular diagnostic work-up, the scanning protocol might vary somewhat between participating centres.

The MRI scans retrieved in the Netherlands will be assessed by 2 neuroradiologist separately, each with multiple years of experience in MRI assessment of head and neck pathology. The MRI scans of patients included in Antwerp will be assessed by a neuroradiologist of the University Hospital Antwerp. Figure 2 shows the scoring sheet used for MRI assessment. In case the degree of white matter hyperintensities differs 2 or more points on the Fazekas scale, the radiologist will review the MRI together until consensus is reached. Previous MRI assessments performed by both radiologists involved in this study demonstrated substantial interrater agreement in white matter hyperintensity assessment using the Fazekas score, with a kappa value of 0.74[25].

Patient and Public Involvement

Patients were not involved in the design of this study. Results from the study will be shared with patients after completion of the study.

Ethics and dissemination

Informed consent

Prior to seeking consent to enter the study, participants will receive an explanation of the study along with an information leaflet, followed by a minimum of 5 days for consideration. Participants have the right to decline participation without the need to provide a specific reason. If patients do not give consent in participating in the study, their contact information will thereafter be deleted from our records.

Data handling

Personal data, including medical history and diagnostic test results, will be sent to the investigating site via digitally protected email, after informed consent has been obtained.

Upon arrival at Gelre Hospital, the relevant information will be extracted from the received files. Subsequently, this data will be pseudonymized and stored in a research database, using Castor EDC (Castor EDC, Amsterdam, The Netherlands). The original files will be stored on a protected data drive at the ADC.

MRI scans obtained from hospitals in the Netherlands will be shared electronically via the national Twiin platform for data exchange, developed by Vereniging van Zorgaanbieders voor Zorgcommunicatie (VZVZ), Den Haag, The Netherlands. The MRI scans will be pseudonymised and uploaded to a secured Picture Archiving and Communication System (PACS) worklist at the radiology department of Gelre Hospital Apeldoorn. Following assessment of the pseudonymised MRI-scans, this PACS worklist will be deleted, while the MRI scans themselves have been stored on a protected data drive of the ADC.

MRI scans from Antwerp will be assessed by their respective neuroradiologists due to data international transfer restrictions.

The assembled document files, digital files and MRI-scans will be saved for a period of 15 years on a protected data drive at the ADC. When this period has passed, all data will be deleted and all files will be destroyed.

Risks and benefits

Participants in this study will not be subjected to any additional study-related interventions beyond standard medical practices, such as MRI scans and audiometric testing, which are typically performed when SSNHL is suspected. No blood investigations or procedures beyond the established iSSNHL treatment guidelines in the Netherlands and Belgium will be included in this study.

Implications for future research

The identification of vascular involvement in the onset of sudden deafness could have serious implications for the current treatment guideline of sudden hearing loss. Specifically, for a subset of patients that appears to have increased cardiovascular comorbidity, consideration of cardiovascular risk management, including anticoagulant administration, could be warranted. If the results of the cross-sectional study, as described in this paper, provide evidence for vascular involvement in the pathophysiology of sudden sensorineural hearing loss, follow-up investigation of the included study population could be beneficial. This follow-up could imply a retrospective investigation of the incidence of stroke in the five years after inclusion in this study.

Data deposition

Upon reasonable request, the dataset and statistical code may be shared. The dataset will not be publicly accessible. To stimulate transparency and improve future research, this protocol will be published open access.

Funding statement

The data will be published according to the STROBE-statement (Strengthening the Reporting of Observational studies in Epidemiology). The funder of this study, Gelre Hospital, will not interfere with public disclosure and publication of the research data. The funder cannot provide a grant/award number.

Competing interest statement

The authors have no competing interest to declare in the study design or execution thereof.

Authors contributions

All authors have contributed to the study design. F. Oussoren, R.B. van Leeuwen and T.D. Bruintjes are responsible for the overall conduct of the study. C. Colijn and F. Oussoren will be responsible for the data collection. F. Oussoren and T. Schermer will be responsible for the statistical analysis. J. Kardux and L. Poulsen will be responsible for the MRI assessment. E. Hensen and M. Lammers will be responsible for the inclusionof the control cohort

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Inclusion criteria sudden deafness cohort	*Inclusion criteria control cohort*
• Sudden deafness defined by acute onset sensorineural hearing loss of at least 30dB on 3 consecutive frequencies occurring withing 72 hours or less. • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years	• Patients diagnosed with trigeminal neuralgia, hemifacial spasm, vestibular paroxysmia or a cerebellopontine neoplasm. • Absence of sudden sensorineural hearing loss • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years
Exclusion criteria	
• Diagnosis of sudden deafness prior to the study period. • Significant cerebral damage due to a pre-existing medical condition that will impede an adequate assessment of the degree of cerebral small vessel disease. For instance, a medical history of multiple sclerosis of systemic vasculitis. • Presence of an enlarged vestibular aqueduct on MRI that could be responsible for SSNHL • An identifiable cause of ~~i~~SSNHL such as a Borrelia Burgdorferi infection.	

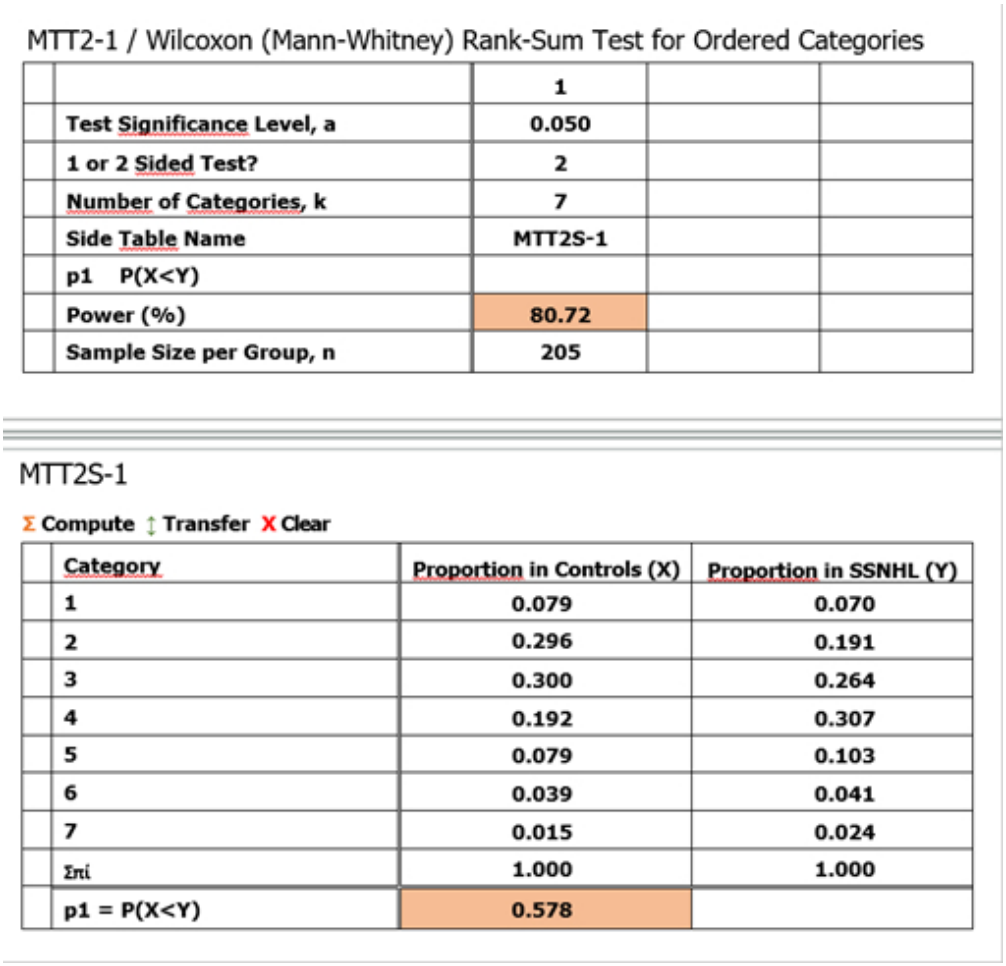
Table 1. Inclusion and exclusion criteria for participation in the ROSALIE study. FLAIR=fluid attenuated inversion recovery, iSSNHL=idiopathic sudden sensorineural hearing loss.

Figure legends

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected

proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

Figure 2. MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.



MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test for Ordered Categories

	1		
Test Significance Level, a	0.050		
1 or 2 Sided Test?	2		
Number of Categories, k	7		
Side Table Name	MTT2S-1		
p1 P(X<Y)			
Power (%)	80.72		
Sample Size per Group, n	205		

MTT2S-1

Σ Compute ↕ Transfer X Clear

Category	Proportion in Controls (X)	Proportion in SSNHL (Y)
1	0.079	0.070
2	0.296	0.191
3	0.300	0.264
4	0.192	0.307
5	0.079	0.103
6	0.039	0.041
7	0.015	0.024
Σπi	1.000	1.000
p1 = P(X<Y)	0.578	

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

134x129mm (96 x 96 DPI)

1. Fazekas score

A. periventricular white matter (PVWM)	
	0 = absent
	1 = "caps" or pencil-thin lining
	2 = smooth "halo"
	3 = irregular periventricular signal extending into the deep white matter
B. deep white matter (DWM)	
	0 = absent
	1 = punctate foci
	2 = beginning confluence
	3 = large confluent areas
	Total: 0 up to 6.

2. (Silent) brain infarctions*

	Yes= 1 / No= 0	Remarks
Presence		
Size (in mm)		

*SBI's need to meet the following criteria:
1. Minimal size of 3mm
2. Cerebrospinal fluid (CSF) appearance in all MRI sequences.
3. Can be differentiated from dilated Virchow-Robin spaces (dVRS)

MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

127x132mm (96 x 96 DPI)

BMJ Open

Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

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Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

Running title: ROSALIE study protocol

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The data will be published according to the STROBE-statement (Strengthening the Reporting of Observational studies in Epidemiology). The sponsor of this study (Gelre Hospital) will not interfere with public disclosure and publication of the research data.

Competing interest statement

The authors have no competing interest to declare in the study design or execution thereof.

Word count: 2290

Abstract

Introduction: The etiology of sudden sensorineural hearing loss (SSNHL) is not certain in a significant number of cases. In 8-31% of posterior fossa infarctions acute hearing or vestibular loss precedes neurologic symptoms. Also, several retrospective cohort analyses have indicated a higher chance of experiencing a stroke after SSNHL compared to the general population. This higher incidence of stroke suggests vascular involvement in the pathophysiology of SSNHL. The aim of this study is to evaluate the association of cardiovascular disease and iSSNHL by investigating the presence of cardiovascular risk factors and cerebral small vessel disease, in patients with idiopathic SSNHL and compare this to controls

Method and analysis: In this multicentre cross-sectional study, 205 patients aged 50 years or higher diagnosed with idiopathic SSNHL, and 205 controls who are either suspected of trigeminus neuralgia, hemifacial spasm, vestibular paroxysmia, or have a cerebellopontine angle neoplasm, will be included. The primary outcome is the difference in cerebral small vessel disease, measured by the degree of white matter hyperintensities according to the Fazekas scale and the presence of brain infarctions on MRI, between patients with idiopathic SSNHL and controls. The secondary outcome is the difference in prevalence of the cardiovascular risk factors: hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction between both cohorts.

Ethics and dissemination: Ethics approval has been obtained by the institutional review boards of all participating hospitals. Patients will receive the standard diagnostic protocol for iSSNHL in the Netherlands; which consists of pure tone audiometric assessment before and after treatment with

corticosteroids and an MRI of the cerebellopontine angle displaying the entire cerebrum. Data will not be available publicly but might be shared upon reasonable request.

Registration:

The Medical Research Involving Human Subjects Act does not apply to this study, as has been declared by the regional review board at Leiden University Hospital, registration number 22-3060.

Keywords:

Sudden deafness, MRI, white matter hyperintensities

Strengths and limitations

Strengths:

- Multicenter study using hospital derived data
- Radiological assessment by two expert neuroradiologists

Limitations:

- MRI sequences might slightly differ between participating centers
- Suspectibility weighted imaging (SWI) is not part of the MRI scanning protocol used and therefore microbleeds could be missed
- MRI Assessment in Antwerp is performed by separate neuroradiologists

Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency, commonly defined as the abrupt onset of sensorineural hearing loss exceeding 30dB in at least 3 contiguous audiometric frequencies, manifesting within a span of 72 hours[1–3].

The annual incidence of SSNHL is approximately 5-20 cases per 100.000 individuals. In 32-72% of the cases the hearing loss recovers spontaneously [4,5]. Unfortunately, in 30-50% percent of cases, hearing loss does not improve after treatment with high-dose corticosteroids, which is the generally accepted treatment modality in the Netherlands, based on the suspicion of an inflammatory etiology [6].

While the etiologic factor in most cases cannot be identified, one hypothesis under examination implicates vascular involvement in the pathophysiology of SSNHL. Given that the internal auditory artery (IAA) is an end artery with little collateral blood supply, the cochlea is particularly susceptible to ischemia [7,8]. Research has focused on the potential link between idiopathic SSNHL (iSSNHL) and systemic cardiovascular disease, aiming to investigate the plausibility of vascular involvement in the pathophysiology of SSNHL. Multiple studies have reported higher prevalences of cardiovascular risk factors, such as smoking, alcohol abuse and hypercholesterolemia, in patients with SSNHL compared to controls.

Additionally, several cohort studies in Taiwan and Korea have reported increased incidence of stroke following iSSNHL[9–1213]. In a meta-analysis, Lammers et al. calculated the hazard risk of developing stroke after experiencing SSNHL to be 1.42[14]. Kim et al. reported that in 8-31% of patients experiencing posterior circulation cerebrovascular accidents (CVA) exhibited preceding hearing or vestibular loss within a month[15]. Sudden hearing loss might therefore be an indicator of stroke and warrant interventions to prevent cardiovascular events, known for their significant morbidity and mortality.

While the exact pathophysiology of cerebral small vessel disease (CSVD) is not clarified, it is widely believed to result from systemic cardiovascular disease, particularly hypertension[16]. The presence of CSVD elevates the risk of stroke and other vascular neurodegenerative conditions, including vascular dementia[17–19]. We hypothesize that patients with iSSNHL will exhibit a higher prevalence of cerebral small vessel disease than healthy individuals, due to their increased cardiovascular comorbidity. CSVD can be visualized on MRI by the presence of white matter hyperintensities (WMH), cerebral microbleeds, lacunes and silent brain infarctions[18].

To investigate this hypothesis, we will conduct a multicenter cross-sectional analysis based on hospital derived data. Our study aims to investigate the presence of WMH and brain infarctions on MRI in elderly patients with iSSNHL, comparing these findings with a carefully matched control cohort. . Additionally, we will compare the prevalence of cardiovascular risk factors and comorbidity between both cohorts.

Method and analysis

Design

Patients will be included within a two-year period starting from may 2023 at participating hospitals in both the Netherlands and Belgium. The participating centres are Gelre Hospital Apeldoorn and Zutphen, Leiden University Medical Centre, Groene Hart hospital Gouda, Rijnstate hospital Arnhem, Treant Emmen, Saint Franciscus Gasthuis Rotterdam, Medisch spectrum Twente, Isala Zwolle, Rivierenland Tiel and the University Hospital of Antwerp. A total of 410 patients will be included, 205 patients with idiopathic SSNHL and 205 subjects without iSSNHL in the control cohort. Patients will be recruited in the participating centres, but all data collection and subsequent analysis will be centralized and conducted at the Apeldoorn Dizziness Centre (ADC).

The ADC, located within the Gelre Hospital location Apeldoorn, serves as a multidisciplinary tertiary referral centre involving the Neurology, Otorhinolaryngology and Clinical Neurophysiology departments. The ADC specialises in the diagnostic and therapeutic workup of Dizziness.

Inclusion

The study cohort will comprise patients diagnosed with iSSNHL and reside within the service areas of participating hospitals. A detailed description of the inclusion and exclusion criteria can be found in table 1.

The control cohort will consist of patients presenting at the ADC or Gelre hospital with suspected diagnoses of trigeminal neuralgia, hemifacial spasm or vestibular paroxysmia, as well as patients with cerebellopontine neoplasms who have been referred to and are treated at the Leiden University Medical Centre or University Hospital of Antwerp.

Sample size calculation

A sample size calculation was conducted using nQuery software (Statsols, San Diego, CA, USA). Since the main outcome variable, the Fazekas score, is an ordinal variable, the sample size was calculated using a Mann-Whitney U rank-sum test with a two-sided significance level of 0.05. To perform this calculation, we used the proportions of patients falling into each Fazekas score category, as was previously observed in our retrospective case-control study comparing cerebral small vessel disease in patients with vestibular neuritis (VN) and a control cohort[20]. The control population in this previous study aligns with literature, where a Fazekas score of 2 is expected in individuals aged 60-70 years[21]. Given our hypothesis of greater cardiovascular comorbidity in patients with SSNHL compared to the general population, we expect the median Fazekas score in the SSNHL patients to be 3.

Figure 1 displays the output of the sample size calculation, demonstrating that the inclusion of 205 patients in each of the two groups (i.e., SSNHL and controls) yields 80.72% power to reject the null hypothesis. This null hypothesis posits that the distribution of patients across the 7 Fazekas categories in the SSNHL cohort and the control cohort is equal (i.e. the latter is derived from our previous study[20] and shown in the bottom part of Figure 1).

Study outcomes

The primary objective of this study is to assess the difference in prevalence of cerebral small vessel disease on MRI between patients diagnosed with iSSNHL and controls. This evaluation is based on two parameters, the extent of white matter hyperintensities, quantified using the Fazekas score and the presence of brain infarctions. The Fazekas score is the most frequently used diagnostic tool to assess the severity of white matter hyper-intensities in both periventricular and deep white matter regions[19,22]. It is an ordinal scale ranging from 0 to 6, see figure 2. Brain infarctions are defined as lesions of the brain with a minimal diameter of 3mm, displaying cerebrospinal fluid like intensity on FLAIR or or T2 MRI sequences and clearly differentiable from leukoaraiosis and dilated Virchow-Robinson spaces[23]

The secondary outcome is the prevalence of the cardiovascular risk factors age, gender, hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction. Hypertension is defined by meeting either of the following criteria: a. having a medical history of physician diagnosed hypertension and/or b. taking antihypertensive drugs. Hypercholesterolemia is defined by meeting either of these criteria: a. having a medical history of physician diagnosed hypercholesterolemia and/or b. the use of lipid-lowering medication. BMI is calculated by dividing the patients' weight in kilogram by the square of their height in meters at the time of iSSNHL diagnosis. Smoking status is recorded as either former,

current or non-smoker. Diabetes is defined by either having a medical history of physician diagnosed diabetes mellitus and/or the use of oral hypoglycemic drugs or insulin.

Aditionally, to account for potential confounding factors, binary and multinomial logistic regression analyses will be performed to compare the primary and secondary outcomes between both cohorts.

Treatment modalities

Corticosteroid therapy

The standard treatment for patients with iSSNHL is an oral corticosteroid regimen, consisting of 1mg/kg/day of prednisolone with a maximum of 60mg, administered for a period of 7 up to 14 days, Subsequently, the dosage is gradually reduced to zero over the same timeframe[24]. In case of a contraindication for oral corticosteroid use, intratympanic corticosteroid therapy is recommended. A 0.4ml to 0.8ml injection of either dexamethasone (10mg/ml) or methylprednisolone (30 to 40mg/ml) is injected into the middle ear every 3 to 7 days, for a maximum of 4 sessions. If no significant improvement in hearing is observed following oral corticosteroid therapy, intratympanic corticosteroid injection can be considered for salvage therapy.

Hyperbaric oxygen therapy

In Belgium, hyperbaric oxygen therapy (HBOT) is commonly used as treatment option for sudden sensorineural hearing loss. Hyperbaric oxygen therapy can either be combined with oral corticosteroids or used as a salvage therapy when corticosteroid therapy fails to resulted in hearing recovery. The procedure involves administering hyperbaric oxygen via a facemask in a pressurized chamber at around 2.5 atmospheres, with each session lasting 90 up to 120 minutes. This session will be repeated 10 times[25,26].

It is important to note that In the Netherlands HBOT is not part of the regular therapeutic workup due to the limited supporting evidence and high costs[27].

Study procedures:

Subject identification and inclusion

Patients eligible for the study cohort will be recruited by their respective Ear, Nose and Throat (ENT) surgeons at participating centres in both The Netherlands and Belgium. Patients eligible for the control cohort will be recruited by neurologists or ENT-surgeons at Gelre Hospital and ENT-surgeons in Leiden University Medical Center and University Hospital Antwerp.

Data collection

Informed consent will be obtained during a telephone interview conducted several days after the patient receives the written patient information about the study. During this telephone interview, the patient will sign the informed consent form and return it to the research team at Gelre Hospitals, through postal mail. The interview will also include the identification of the patient's symptoms at the onset of iSSNHL, verification of their medical history and medication use.

Once the signed informed consent form is received by the coordinating investigator, relevant data from the participating hospitals will be sought. This data includes the patient's age, weight, height, medical history, current medication uses and their most recent MRI scan. MRI scans from University Hospital Antwerp will not be shared due to international data transfer restrictions. For the SSNHL cohort, results from pure tone audiometric tests conducted before and after corticosteroid therapy, as well as results from video-head impulse testing and/or calorimetric tests, if performed, will be gathered. Additionally, details regarding the received treatment strategy will be collected.

MRI assessment

MRI scans will be included in the study if they were performed within six months prior to the onsef of sudden deafness or within 3 months afterwards. In order to be adequately analysed, the MRI requires either a T2 or FLAIR sequence of the entire brain. While an MRI of the cerebellopontine angle or entire brain is part of regular diagnostic work-up, the scanning protocol might vary somewhat between participating centres. The scanning protocol including types of sequences used, TR times, TE times, Voxel size, rotation and slice thickness for each patients will be documented upon finalisation of the study. Susceptibility weighted imaging is commonly included in the scanning protocol of the MRI's included in our study. The main limitation thereof is included in the limitation section.

The MRI scans retrieved in the Netherlands will be assessed by 2 neuroradiologist separately, each with multiple years of experience in MRI assessment of head and neck pathology. The radiologists will be blinded for clinical data. The MRI scans of patients included in Antwerp will be assessed by a neuroradiologist of the University Hospital Antwerp. Figure 2 shows the scoring sheet used for MRI assessment. In case the degree of white matter hyperintensities differs 2 or more points on the Fazekas scale, the radiologist will review the MRI together until consensus is reached. Previous MRI assessments performed by both radiologists involved in this study demonstrated substantial interrater agreement in white matter hyperintensity assessment using the Fazekas score, with a kappa value of 0.74[20].

Ethics and dissemination

The Medical Research Involving Human Subjects Act does not apply to this study, as has been declared by the regional review board at Leiden University Hospital, registration number 22-3060.

Ethical approval for participation has been obtained by the institutional review boards of all participating hospitals prior to the start of the study.

Informed consent

Prior to seeking consent to enter the study, participants will receive an explanation of the study along with an information leaflet, followed by a minimum of 5 days for consideration. Participants have the right to decline participation without the need to provide a specific reason. If patients do not give consent in participating in the study, their contact information will thereafter be deleted from our records.

Data handling

Personal data, including medical history and diagnostic test results, will be sent to the investigating site via digitally protected email, after informed consent has been obtained.

Upon arrival at Gelre Hospital, the relevant information will be extracted from the received files. Subsequently, this data will be pseudonymized and stored in a research database, using Castor EDC (Castor EDC, Amsterdam, The Netherlands). The original files will be stored on a protected data drive at the ADC.

MRI scans obtained from hospitals in the Netherlands will be shared electronically via the national Twiin platform for data exchange, developed by Vereniging van Zorgaanbieders voor Zorgcommunicatie (VZVZ), Den Haag, The Netherlands. The MRI scans will be pseudonymised and uploaded to a secured Picture Archiving and Communication System (PACS) worklist at the radiology department of Gelre Hospital Apeldoorn. Following assessment of the pseudonymised MRI-scans, this PACS worklist will be deleted, while the MRI scans themselves have been stored on a protected data drive of the ADC.

MRI scans from Antwerp will be assessed by their respective neuroradiologists due to data international transfer restrictions.

The assembled document files, digital files and MRI-scans will be saved for a period of 15 years on a protected data drive at the ADC. When this period has passed, all data will be deleted and all files will be destroyed.

Risks and benefits

Participants in this study will not be subjected to any additional study-related interventions beyond standard medical practices, such as MRI scans and audiometric testing, which are typically performed when SSNHL is suspected. No blood investigations or procedures beyond the established iSSNHL treatment guidelines in the Netherlands and Belgium will be included in this study.

Implications for future research

The identification of vascular involvement in the onset of sudden deafness could have serious implications for the current treatment guideline of sudden hearing loss. Specifically, for a subset of patients that appears to have increased cardiovascular comorbidity, consideration of cardiovascular risk management, including anticoagulant administration, could be warranted. If the results of the cross-sectional study, as described in this paper, provide evidence for vascular involvement in the pathophysiology of sudden sensorineural hearing loss, follow-up investigation of the included study population could be beneficial. This follow-up could imply a retrospective investigation of the incidence of stroke in the five years after inclusion in this study.

Data deposition

Upon reasonable request, the dataset and statistical code may be shared. The dataset will not be publicly accessible. To stimulate transparency and improve future research, this protocol will be published open access.

Patient involvement

There was no patient involvement in the design of the study.

Authors contributions

All authors have contributed to the study design. F.K. Oussoren, R.B. van Leeuwen and T.D. Bruintjes are responsible for the overall conduct of the study. C. Colijn and F. Oussoren will be responsible for the data collection. F. Oussoren and T. Schermer will be responsible for the statistical analysis. J. Kardux and L. Poulsen will be responsible for the MRI assessment. E. Hensen and M. Lammers will be responsible for the of the control cohort

Funding and competing interest

The guarantor of the study is prof. dr. T.D. Bruintjes and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Tables

Inclusion criteria sudden deafness cohort	*Inclusion criteria control cohort*
• Sudden deafness defined by acute onset sensorineural hearing loss of at least 30dB on 3 consecutive frequencies occurring withing 72 hours or less. • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years	• Patients diagnosed with trigeminal neuralgia, hemifacial spasm, vestibular paroxysmia or a cerebellopontine neoplasm. • Absence of sudden sensorineural hearing loss • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years
Exclusion criteria	
• Diagnosis of sudden deafness prior to the study period.	

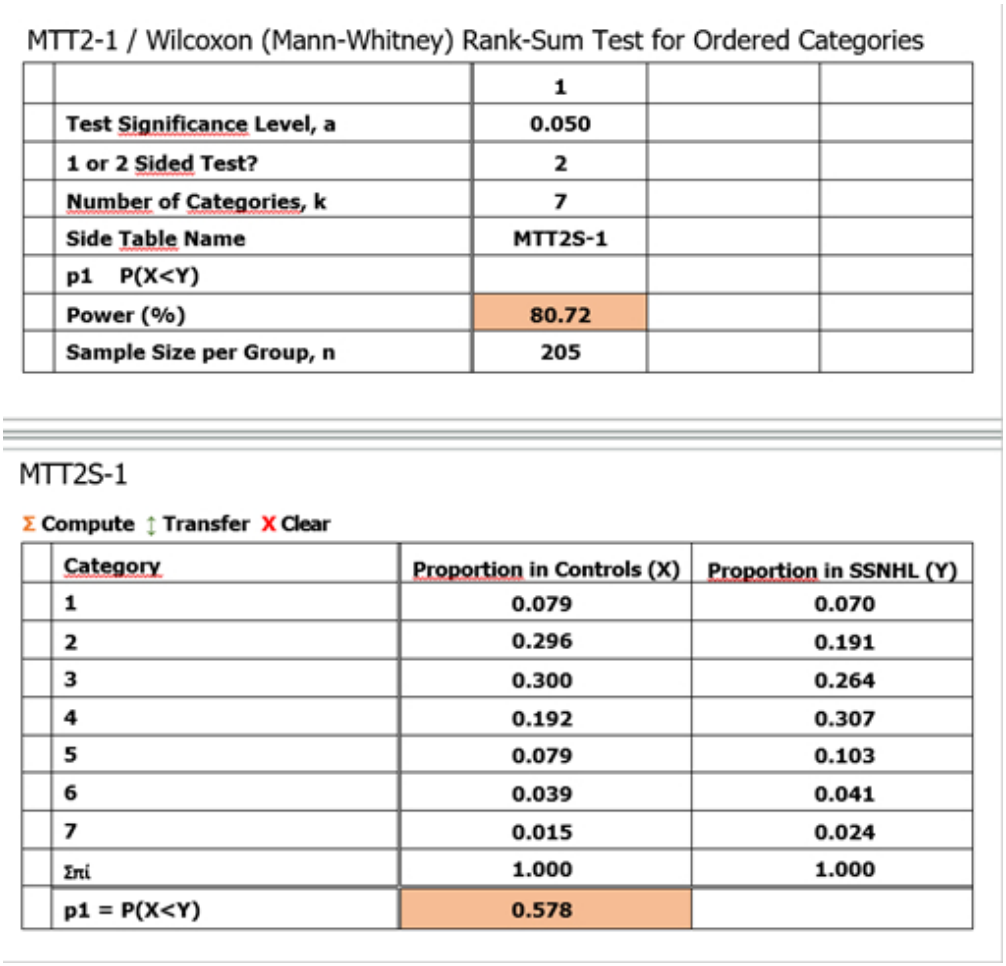
• Significant cerebral damage due to a pre-existing medical condition that will impede an adequate assessment of the degree of cerebral small vessel disease. For instance, a medical history of multiple sclerosis. • Presence of an enlarged vestibular aqueduct on MRI that could be responsible for SSNHL • An identifiable cause of ~~i~~SSNHL such as a Borrelia Burgdorferi infection.

Table 1. Inclusion and exclusion criteria for participation in the ROSALIE study. FLAIR=fluid attenuated inversion recovery, iSSNHL=idiopathic sudden sensorineural hearing loss.

Figure legends

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

Figure 2. MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.



MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test for Ordered Categories

	1		
Test Significance Level, a	0.050		
1 or 2 Sided Test?	2		
Number of Categories, k	7		
Side Table Name	MTT2S-1		
p1 P(X<Y)			
Power (%)	80.72		
Sample Size per Group, n	205		

MTT2S-1

Σ Compute ↕ Transfer X Clear

Category	Proportion in Controls (X)	Proportion in SSNHL (Y)
1	0.079	0.070
2	0.296	0.191
3	0.300	0.264
4	0.192	0.307
5	0.079	0.103
6	0.039	0.041
7	0.015	0.024
Σπi	1.000	1.000
p1 = P(X<Y)	0.578	

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

134x129mm (96 x 96 DPI)

1. Fazekas score

A. periventricular white matter (PVWM)	
	0 = absent
	1 = "caps" or pencil-thin lining
	2 = smooth "halo"
	3 = irregular periventricular signal extending into the deep white matter
B. deep white matter (DWM)	
	0 = absent
	1 = punctate foci
	2 = beginning confluence
	3 = large confluent areas
	Total: 0 up to 6.

2. (Silent) brain infarctions*

	Yes= 1 / No= 0	Remarks
Presence		
Size (in mm)		

*SBI's need to meet the following criteria:
1. Minimal size of 3mm
2. Cerebrospinal fluid (CSF) appearance in all MRI sequences.
3. Can be differentiated from dilated Virchow-Robin spaces (dVRS)

MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

127x132mm (96 x 96 DPI)

BMJ Open

Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

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Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

Running title: ROSALIE study protocol

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The data will be published according to the STROBE-statement (Strengthening the Reporting of Observational studies in Epidemiology). The sponsor of this study (Gelre Hospital) will not interfere with public disclosure and publication of the research data.

Competing interest statement

The authors have no competing interest to declare in the study design or execution thereof.

Word count: 2290

Abstract

Introduction: The etiology of sudden sensorineural hearing loss (SSNHL) is not certain in a significant number of cases. In 8-31% of posterior fossa infarctions acute hearing or vestibular loss precedes neurologic symptoms. Also, several retrospective cohort analyses have indicated a higher chance of experiencing a stroke after SSNHL compared to the general population. This higher incidence of stroke suggests vascular involvement in the pathophysiology of SSNHL. The aim of this study is to evaluate the association of cardiovascular disease and iSSNHL by investigating the presence of cardiovascular risk factors and cerebral small vessel disease, in patients with idiopathic SSNHL and compare this to controls

Method and analysis: In this multicentre cross-sectional study, 205 patients aged 50 years or higher diagnosed with idiopathic SSNHL, and 205 controls who are either suspected of trigeminus neuralgia, hemifacial spasm, vestibular paroxysmia, or have a cerebellopontine angle neoplasm, will be included. The primary outcome is the difference in cerebral small vessel disease, measured by the degree of white matter hyperintensities according to the Fazekas scale and the presence of brain infarctions on MRI, between patients with idiopathic SSNHL and controls. The secondary outcome is the difference in prevalence of the cardiovascular risk factors: hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction between both cohorts.

Ethics and dissemination: Ethics approval has been obtained by the institutional review boards of all participating hospitals. Patients will receive the standard diagnostic protocol for iSSNHL in the Netherlands; which consists of pure tone audiometric assessment before and after treatment with corticosteroids and an MRI of the cerebellopontine angle displaying the entire cerebrum. Data will not be available publicly but might be shared upon reasonable request.

Strengths and limitations

Strengths:

- Multicenter study using hospital derived data
- Radiological assessment by two expert neuroradiologists

Limitations:

- MRI sequences might slightly differ between participating centers
- In patients whose hearing has recovered by the time the MRI scan is scheduled will not be included in the study
- MRI Assessment in Antwerp is performed by separate neuroradiologists

Keywords:

Sudden deafness, MRI, white matter hyperintensities

Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency, commonly defined as the abrupt onset of sensorineural hearing loss exceeding 30dB in at least 3 contiguous audiometric frequencies, manifesting within a span of 72 hours[1–3].

The annual incidence of SSNHL is approximately 5-20 cases per 100.000 individuals. In 32-72% of the cases the hearing loss recovers spontaneously [4,5]. Unfortunately, in 30-50% percent of cases, hearing loss does not improve after treatment with high-dose corticosteroids, which is the generally accepted treatment modality in the Netherlands, based on the suspicion of an inflammatory etiology [6].

While the etiologic factor in most cases cannot be identified, one hypothesis under examination implicates vascular involvement in the pathophysiology of SSNHL. Given that the internal auditory artery (IAA) is an end artery with little collateral blood supply, the cochlea is particularly susceptible to ischemia [7,8]. Research has focused on the potential link between idiopathic SSNHL (iSSNHL) and systemic cardiovascular disease, aiming to investigate the plausibility of vascular involvement in the pathophysiology of SSNHL. Multiple studies have reported higher prevalences of cardiovascular risk factors, such as smoking, alcohol abuse and hypercholesterolemia, in patients with SSNHL compared to controls.

Additionally, several cohort studies in Taiwan and Korea have reported increased incidence of stroke following iSSNHL[9–1213]. In a meta-analysis, Lammers et al. calculated the hazard risk of developing stroke after experiencing SSNHL to be 1.42[14]. Kim et al. reported that in 8-31% of patients experiencing posterior circulation cerebrovascular accidents (CVA) exhibited preceding hearing or vestibular loss within a month[15]. Sudden hearing loss might therefore be an indicator of stroke and warrant interventions to prevent cardiovascular events, known for their significant morbidity and mortality.

While the exact pathophysiology of cerebral small vessel disease (CSVD) is not clarified, it is widely believed to result from systemic cardiovascular disease, particularly hypertension[16]. The presence of CSVD elevates the risk of stroke and other vascular neurodegenerative conditions, including vascular dementia[17–19]. We hypothesize that patients with iSSNHL will exhibit a higher prevalence of cerebral small vessel disease than healthy individuals, due to their increased cardiovascular comorbidity. CSVD can be visualized on MRI by the presence of white matter hyperintensities (WMH), cerebral microbleeds, lacunes and silent brain infarctions[18].

To investigate this hypothesis, we will conduct a multicenter cross-sectional analysis based on hospital derived data. Our study aims to investigate the presence of WMH and brain infarctions on MRI in elderly patients with iSSNHL, comparing these findings with a carefully matched control cohort. . Additionally, we will compare the prevalence of cardiovascular risk factors and comorbidity between both cohorts.

Method and analysis

Design

Patients will be included within a two-year period starting from may 2023 at participating hospitals in both the Netherlands and Belgium. The participating centres are Gelre Hospital Apeldoorn and Zutphen, Leiden University Medical Centre, Groene Hart hospital Gouda, Rijnstate hospital Arnhem, Treant Emmen, Saint Franciscus Gasthuis Rotterdam, Medisch spectrum Twente, Isala Zwolle, Rivierenland Tiel and the University Hospital of Antwerp. A total of 410 patients will be included, 205 patients with idiopathic SSNHL and 205 subjects without iSSNHL in the control cohort. Patients will be recruited in the participating centres, but all data collection and subsequent analysis will be centralized and conducted at the Apeldoorn Dizziness Centre (ADC).

The ADC, located within the Gelre Hospital location Apeldoorn, serves as a multidisciplinary tertiary referral centre involving the Neurology, Otorhinolaryngology and Clinical Neurophysiology departments. The ADC specialises in the diagnostic and therapeutic workup of Dizziness.

Inclusion

The study cohort will comprise patients diagnosed with iSSNHL and reside within the service areas of participating hospitals. A detailed description of the inclusion and exclusion criteria can be found in table 1.

The control cohort will consist of patients presenting at the ADC or Gelre hospital with suspected diagnoses of trigeminal neuralgia, hemifacial spasm or vestibular paroxysmia, as well as patients with cerebellopontine neoplasms who have been referred to and are treated at the Leiden University Medical Centre or University Hospital of Antwerp.

Sample size calculation

A sample size calculation was conducted using nQuery software (Statsols, San Diego, CA, USA). Since the main outcome variable, the Fazekas score, is an ordinal variable, the sample size was calculated using a Mann-Whitney U rank-sum test with a two-sided significance level of 0.05. To perform this calculation, we used the proportions of patients falling into each Fazekas score category, as was previously observed in our retrospective case-control study comparing cerebral small vessel disease in patients with vestibular neuritis (VN) and a control cohort[20]. The control population in this previous study aligns with literature, where a Fazekas score of 2 is expected in individuals aged 60-70 years[21]. Given our hypothesis of greater cardiovascular comorbidity in patients with SSNHL compared to the general population, we expect the median Fazekas score in the SSNHL patients to be 3.

Figure 1 displays the output of the sample size calculation, demonstrating that the inclusion of 205 patients in each of the two groups (i.e., SSNHL and controls) yields 80.72% power to reject the null hypothesis. This null hypothesis posits that the distribution of patients across the 7 Fazekas categories in the SSNHL cohort and the control cohort is equal (i.e. the latter is derived from our previous study[20] and shown in the bottom part of Figure 1).

Study outcomes

The primary objective of this study is to assess the difference in prevalence of cerebral small vessel disease on MRI between patients diagnosed with iSSNHL and controls. This evaluation is based on two parameters, the extent of white matter hyperintensities, quantified using the Fazekas score and the presence of brain infarctions. The Fazekas score is the most frequently used diagnostic tool to assess the severity of white matter hyper-intensities in both periventricular and deep white matter regions[19,22]. It is an ordinal scale ranging from 0 to 6, see figure 2. Brain infarctions are defined as lesions of the brain with a minimal diameter of 3mm, displaying cerebrospinal fluid like intensity on FLAIR or or T2 MRI sequences and clearly differentiable from leukoaraiosis and dilated Virchow-Robinson spaces[23]

The secondary outcome is the prevalence of the cardiovascular risk factors age, gender, hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction. Hypertension is defined by meeting either of the following criteria: a. having a medical history of physician diagnosed hypertension and/or b. taking antihypertensive drugs. Hypercholesterolemia is defined by meeting either of these criteria: a. having a medical history of physician diagnosed hypercholesterolemia and/or b. the use of lipid-lowering medication. BMI is calculated by dividing the patients' weight in kilogram by the square of their height in meters at the time of iSSNHL diagnosis. Smoking status is recorded as either former,

current or non-smoker. Diabetes is defined by either having a medical history of physician diagnosed diabetes mellitus and/or the use of oral hypoglycemic drugs or insulin.

Aditionally, to account for potential confounding factors, binary and multinomial logistic regression analyses will be performed to compare the primary and secondary outcomes between both cohorts.

Treatment modalities

Corticosteroid therapy

The standard treatment for patients with iSSNHL is an oral corticosteroid regimen, consisting of 1mg/kg/day of prednisolone with a maximum of 60mg, administered for a period of 7 up to 14 days, Subsequently, the dosage is gradually reduced to zero over the same timeframe[24]. In case of a contraindication for oral corticosteroid use, intratympanic corticosteroid therapy is recommended. A 0.4ml to 0.8ml injection of either dexamethasone (10mg/ml) or methylprednisolone (30 to 40mg/ml) is injected into the middle ear every 3 to 7 days, for a maximum of 4 sessions. If no significant improvement in hearing is observed following oral corticosteroid therapy, intratympanic corticosteroid injection can be considered for salvage therapy.

Hyperbaric oxygen therapy

In Belgium, hyperbaric oxygen therapy (HBOT) is commonly used as treatment option for sudden sensorineural hearing loss. Hyperbaric oxygen therapy can either be combined with oral corticosteroids or used as a salvage therapy when corticosteroid therapy fails to resulted in hearing recovery. The procedure involves administering hyperbaric oxygen via a facemask in a pressurized chamber at around 2.5 atmospheres, with each session lasting 90 up to 120 minutes. This session will be repeated 10 times[25,26].

It is important to note that In the Netherlands HBOT is not part of the regular therapeutic workup due to the limited supporting evidence and high costs[27].

Study procedures:

Subject identification and inclusion

Patients eligible for the study cohort will be recruited by their respective Ear, Nose and Throat (ENT) surgeons at participating centres in both The Netherlands and Belgium. Patients eligible for the control cohort will be recruited by neurologists or ENT-surgeons at Gelre Hospital and ENT-surgeons in Leiden University Medical Center and University Hospital Antwerp.

Data collection

Informed consent will be obtained during a telephone interview conducted several days after the patient receives the written patient information about the study. During this telephone interview, the patient will sign the informed consent form and return it to the research team at Gelre Hospitals, through postal mail. The interview will also include the identification of the patient's symptoms at the onset of iSSNHL, verification of their medical history and medication use.

Once the signed informed consent form is received by the coordinating investigator, relevant data from the participating hospitals will be sought. This data includes the patient's age, weight, height, medical history, current medication uses and their most recent MRI scan. MRI scans from University Hospital Antwerp will not be shared due to international data transfer restrictions. For the SSNHL cohort, results from pure tone audiometric tests conducted before and after corticosteroid therapy, as well as results from video-head impulse testing and/or calorimetric tests, if performed, will be gathered. Additionally, details regarding the received treatment strategy will be collected.

MRI assessment

MRI scans will be included in the study if they were performed within six months prior to the onsef of sudden deafness or within 3 months afterwards. In order to be adequately analysed, the MRI requires either a T2 or FLAIR sequence of the entire brain. While an MRI of the cerebellopontine angle or entire brain is part of regular diagnostic work-up, the scanning protocol might vary somewhat between participating centres. The scanning protocol including types of sequences used, TR times, TE times, Voxel size, rotation and slice thickness for each patients will be documented upon finalisation of the study. Susceptibility weighted imaging is commonly included in the scanning protocol of the MRI's included in our study. The main limitation thereof is included in the limitation section.

The MRI scans retrieved in the Netherlands will be assessed by 2 neuroradiologist separately, each with multiple years of experience in MRI assessment of head and neck pathology. The radiologists will be blinded for clinical data. The MRI scans of patients included in Antwerp will be assessed by a neuroradiologist of the University Hospital Antwerp. Figure 2 shows the scoring sheet used for MRI assessment. In case the degree of white matter hyperintensities differs 2 or more points on the Fazekas scale, the radiologist will review the MRI together until consensus is reached. Previous MRI assessments performed by both radiologists involved in this study demonstrated substantial interrater agreement in white matter hyperintensity assessment using the Fazekas score, with a kappa value of 0.74[20].

Ethics and dissemination

The Medical Research Involving Human Subjects Act does not apply to this study, as has been declared by the regional review board at Leiden University Hospital, registration number 22-3060. Ethical approval for participation has been obtained by the institutional review boards of all

participating hospitals prior to the start of the study. The study received the following registration numbers according to participating centre: Leiden University Hospital: 22-3060; Gelre Hospital: 2022.47 ; Groene Hart Hospital: LI-2023-05; Isala Hospital: 20230413; Medisch spectrum Twente: KH23-23; Rijnstate hospital: 2023-2207; Treant Emmen:2023-16.

The final results of the study are planned to be published in an open access journal after completion of analyses. For information regarding deposition of data, see the separate section.

Informed consent

Prior to seeking consent to enter the study, participants will receive an explanation of the study along with an information leaflet, followed by a minimum of 5 days for consideration. Participants have the right to decline participation without the need to provide a specific reason. If patients do not give consent in participating in the study, their contact information will thereafter be deleted from our records.

Data handling

Personal data, including medical history and diagnostic test results, will be sent to the investigating site via digitally protected email, after informed consent has been obtained.

Upon arrival at Gelre Hospital, the relevant information will be extracted from the received files. Subsequently, this data will be pseudonymized and stored in a research database, using Castor EDC (Castor EDC, Amsterdam, The Netherlands). The original files will be stored on a protected data drive at the ADC.

MRI scans obtained from hospitals in the Netherlands will be shared electronically via the national Twiin platform for data exchange, developed by Vereniging van Zorgaanbieders voor Zorgcommunicatie (VZVZ), Den Haag, The Netherlands. The MRI scans will be pseudonymised and

uploaded to a secured Picture Archiving and Communication System (PACS) worklist at the radiology department of Gelre Hospital Apeldoorn. Following assessment of the pseudonymised MRI-scans, this PACS worklist will be deleted, while the MRI scans themselves have been stored on a protected data drive of the ADC.

MRI scans from Antwerp will be assessed by their respective neuroradiologists due to data international transfer restrictions.

The assembled document files, digital files and MRI-scans will be saved for a period of 15 years on a protected data drive at the ADC. When this period has passed, all data will be deleted and all files will be destroyed.

Risks and benefits

Participants in this study will not be subjected to any additional study-related interventions beyond standard medical practices, such as MRI scans and audiometric testing, which are typically performed when SSNHL is suspected. No blood investigations or procedures beyond the established iSSNHL treatment guidelines in the Netherlands and Belgium will be included in this study.

Implications for future research

The identification of vascular involvement in the onset of sudden deafness could have serious implications for the current treatment guideline of sudden hearing loss. Specifically, for a subset of patients that appears to have increased cardiovascular comorbidity, consideration of cardiovascular risk management, including anticoagulant administration, could be warranted. If the results of the cross-sectional study, as described in this paper, provide evidence for vascular involvement in the pathophysiology of sudden sensorineural hearing loss, follow-up investigation of the included study

population could be beneficial. This follow-up could imply a retrospective investigation of the incidence of stroke in the five years after inclusion in this study.

Data deposition

Upon reasonable request, the dataset and statistical code may be shared by contacting the primary author. The dataset will not be publicly accessible. To stimulate transparency and improve future research, this protocol will be published open access.

Patient and public involvement

Patients or the public were not involved in the design, the conduct, the reporting or the disseminations plans of our research.

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Tables

Inclusion criteria sudden deafness cohort	*Inclusion criteria control cohort*
• Sudden deafness defined by acute onset sensorineural hearing loss of at least 30dB on 3 consecutive frequencies occurring withing 72 hours or less. • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years	• Patients diagnosed with trigeminal neuralgia, hemifacial spasm, vestibular paroxysmia or a cerebellopontine neoplasm. • Absence of sudden sensorineural hearing loss • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years
Exclusion criteria	
• Diagnosis of sudden deafness prior to the study period. • Significant cerebral damage due to a pre-existing medical condition that will impede an adequate assessment of the degree of cerebral small vessel disease. For instance, a medical history of multiple sclerosis. • Presence of an enlarged vestibular aqueduct on MRI that could be responsible for SSNHL • An identifiable cause of ~~i~~SSNHL such as a Borrelia Burgdorferi infection.	

Table 1. Inclusion and exclusion criteria for participation in the ROSALIE study. FLAIR=fluid attenuated inversion recovery, iSSNHL=idiopathic sudden sensorineural hearing loss.

Figure legends

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

Figure 2. MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

Authors contributions

All authors have contributed to the study design. F. Oussoren and T.D. Bruintjes are responsible for the overall conduct of the study. C. Colijn and F. Oussoren will be responsible for the data collection. F. Oussoren and T. Schermer will be responsible for the statistical analysis. J. Kardux and L. Poulsen will be responsible for the MRI assessment. E. Hensen and M. Lammers will be responsible for the of the control cohort

MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test for Ordered Categories

		1		
	Test Significance Level, a	0.050		
	1 or 2 Sided Test?	2		
	Number of Categories, k	7		
	Side Table Name	MTT2S-1		
	p1 P(X<Y)			
	Power (%)	80.72		
	Sample Size per Group, n	205		

MTT2S-1

Σ Compute ↕ Transfer X Clear

	Category	Proportion in Controls (X)	Proportion in SSNHL (Y)
	1	0.079	0.070
	2	0.296	0.191
	3	0.300	0.264
	4	0.192	0.307
	5	0.079	0.103
	6	0.039	0.041
	7	0.015	0.024
	Σπί	1.000	1.000
	p1 = P(X<Y)	0.578	

1. Fazekas score

A. periventricular white matter (PVWM)	
	0 = absent
	1 = “caps” or pencil-thin lining
	2 = smooth “halo”
	3 = irregular periventricular signal extending into the deep white matter
B. deep white matter (DWM)	
	0 = absent
	1 = punctate foci
	2 = beginning confluence
	3 = large confluent areas
	Total: 0 up to 6.

2. Silent brain infarctions*

	Yes= 1 / No= 0	Remarks
Presence		
Size (in mm)		

*SBI’s need to meet the following criteria:

1. Minimal size of 3mm
2. Cerebrospinal fluid (CSF) appearance in all MRI sequences.
3. Can be differentiated from dilated Virchow-Robin spaces (dVRS)

BMJ Open

Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

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Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study.

Running title: ROSALIE study protocol

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The data will be published according to the STROBE-statement (Strengthening the Reporting of Observational studies in Epidemiology). The sponsor of this study (Gelre Hospital) will not interfere with public disclosure and publication of the research data.

Competing interest statement

The authors have no competing interest to declare in the study design or execution thereof.

Word count: 2526

Abstract

Introduction: The etiology of sudden sensorineural hearing loss (SSNHL) is not certain in a significant number of cases. In 8-31% of posterior fossa infarctions acute hearing or vestibular loss precedes neurologic symptoms. Also, several retrospective cohort analyses have indicated a higher chance of experiencing a stroke after SSNHL compared to the general population. This higher incidence of stroke suggests vascular involvement in the pathophysiology of SSNHL. The aim of this study is to evaluate the association of cardiovascular disease and iSSNHL by investigating the presence of cardiovascular risk factors and cerebral small vessel disease, in patients with idiopathic SSNHL and compare this to controls

Method and analysis: In this multicentre cross-sectional study, 205 patients aged 50 years or higher diagnosed with idiopathic SSNHL, and 205 controls who are either suspected of trigeminus neuralgia, hemifacial spasm, vestibular paroxysmia, or have a cerebellopontine angle neoplasm, will be included. The primary outcome is the difference in cerebral small vessel disease, measured by the degree of white matter hyperintensities according to the Fazekas scale and the presence of brain infarctions on MRI, between patients with idiopathic SSNHL and controls. The secondary outcome is the difference in prevalence of the cardiovascular risk factors: hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction between both cohorts.

Ethics and dissemination: Ethics approval has been obtained by the institutional review boards of all participating hospitals. Patients will receive the standard diagnostic protocol for iSSNHL in the Netherlands; which consists of pure tone audiometric assessment before and after treatment with corticosteroids and an MRI of the cerebellopontine angle displaying the entire cerebrum. Data will not be available publicly but might be shared upon reasonable request.

Strengths and limitations

Strengths:

- Multicenter study using hospital derived data
- Radiological assessment by two expert neuroradiologists

Limitations:

- MRI sequences might slightly differ between participating centers
- In patients whose hearing has recovered by the time the MRI scan is scheduled will not be included in the study

Keywords:

Sudden deafness, MRI, white matter hyperintensities

Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency, commonly defined as the abrupt onset of sensorineural hearing loss exceeding 30dB in at least 3 contiguous audiometric frequencies, manifesting within a span of 72 hours[1–3].

The annual incidence of SSNHL is approximately 5-20 cases per 100.000 individuals. In 32-72% of the cases the hearing loss recovers spontaneously [4,5]. Unfortunately, in 30-50% percent of cases, hearing loss does not improve after treatment with high-dose corticosteroids, which is the generally accepted treatment modality in the Netherlands, based on the suspicion of an inflammatory etiology [6].

While the etiologic factor in most cases cannot be identified, one hypothesis under examination implicates vascular involvement in the pathophysiology of SSNHL. Given that the internal auditory artery (IAA) is an end artery with little collateral blood supply, the cochlea is particularly susceptible to ischemia [7,8]. Research has focused on the potential link between idiopathic SSNHL (iSSNHL) and systemic cardiovascular disease, aiming to investigate the plausibility of vascular involvement in the pathophysiology of SSNHL. Multiple studies have reported higher prevalences of cardiovascular risk factors, such as smoking, alcohol abuse and hypercholesterolemia, in patients with SSNHL compared to controls.

Additionally, several cohort studies in Taiwan and Korea have reported increased incidence of stroke following iSSNHL[9–1213]. In a meta-analysis, Lammers et al. calculated the hazard risk of developing stroke after experiencing SSNHL to be 1.42[14]. Kim et al. reported that in 8-31% of patients experiencing posterior circulation cerebrovascular accidents (CVA) exhibited preceding hearing or vestibular loss within a month[15]. Sudden hearing loss might therefore be an indicator of stroke and warrant interventions to prevent cardiovascular events, known for their significant morbidity and mortality.

While the exact pathophysiology of cerebral small vessel disease (CSVD) is not clarified, it is widely believed to result from systemic cardiovascular disease, particularly hypertension[16]. The presence of CSVD elevates the risk of stroke and other vascular neurodegenerative conditions, including vascular dementia[17–19]. We hypothesize that patients with iSSNHL will exhibit a higher prevalence of cerebral small vessel disease than healthy individuals, due to their increased cardiovascular comorbidity. CSVD can be visualized on MRI by the presence of white matter hyperintensities (WMH), cerebral microbleeds, lacunes and silent brain infarctions[18].

To investigate this hypothesis, we will conduct a multicenter cross-sectional analysis based on hospital derived data. Our study aims to investigate the presence of WMH and brain infarctions on MRI in elderly patients with iSSNHL, comparing these findings with a carefully matched control cohort. . Additionally, we will compare the prevalence of cardiovascular risk factors and comorbidity between both cohorts.

Method and analysis

Design

Patients will be included within a two-year period starting from may 2023 at participating hospitals in the Netherlands. The participating centres are Gelre Hospital Apeldoorn and Zutphen, Leiden University Medical Centre, Groene Hart hospital Gouda, Rijnstate hospital Arnhem, Treant Emmen, Saint Franciscus Gasthuis Rotterdam, Medisch spectrum Twente, Isala Zwolle and Rivierenland Tiel. A total of 410 patients will be included, 205 patients with idiopathic SSNHL and 205 subjects without iSSNHL in the control cohort. Patients will be recruited in the participating centres, but all data collection and subsequent analysis will be centralized and conducted at the Apeldoorn Dizziness Centre (ADC).

The ADC, located within the Gelre Hospital location Apeldoorn, serves as a multidisciplinary tertiary referral centre involving the Neurology, Otorhinolaryngology and Clinical Neurophysiology departments. The ADC specialises in the diagnostic and therapeutic workup of Dizziness.

Inclusion

The study cohort will comprise patients diagnosed with iSSNHL and reside within the service areas of participating hospitals. A detailed description of the inclusion and exclusion criteria can be found in table 1.

The control cohort will consist of patients presenting at the ADC or Gelre hospital with suspected diagnoses of trigeminal neuralgia, hemifacial spasm or vestibular paroxysmia, as well as patients with cerebellopontine neoplasms who have been referred to and are treated at the Leiden University Medical Centre.

Sample size calculation

A sample size calculation was conducted using nQuery software (Statsols, San Diego, CA, USA). Since the main outcome variable, the Fazekas score, is an ordinal variable, the sample size was calculated using a Mann-Whitney U rank-sum test with a two-sided significance level of 0.05. To perform this calculation, we used the proportions of patients falling into each Fazekas score category, as was previously observed in our retrospective case-control study comparing cerebral small vessel disease in patients with vestibular neuritis (VN) and a control cohort[20]. The control population in this previous study aligns with literature, where a Fazekas score of 2 is expected in individuals aged 60-70 years[21]. Given our hypothesis of greater cardiovascular comorbidity in patients with SSNHL compared to the general population, we expect the median Fazekas score in the SSNHL patients to be 3.

Figure 1 displays the output of the sample size calculation, demonstrating that the inclusion of 205 patients in each of the two groups (i.e., SSNHL and controls) yields 80.72% power to reject the null hypothesis. This null hypothesis posits that the distribution of patients across the 7 Fazekas categories in the SSNHL cohort and the control cohort is equal (i.e. the latter is derived from our previous study[20] and shown in the bottom part of Figure 1).

Study outcomes

The primary objective of this study is to assess the difference in prevalence of cerebral small vessel disease on MRI between patients diagnosed with iSSNHL and controls. This evaluation is based on two parameters, the extent of white matter hyperintensities, quantified using the Fazekas score and the presence of brain infarctions. The Fazekas score is the most frequently used diagnostic tool to assess the severity of white matter hyper-intensities in both periventricular and deep white matter regions[19,22]. It is an ordinal scale ranging from 0 to 6, see figure 2. Brain infarctions are defined as lesions of the brain with a minimal diameter of 3mm, displaying cerebrospinal fluid like intensity on FLAIR or or T2 MRI sequences and clearly differentiable from leukoaraiosis and dilated Virchow-Robinson spaces[23]

The secondary outcome is the prevalence of the cardiovascular risk factors age, gender, hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction. Hypertension is defined by meeting either of the following criteria: a. having a medical history of physician diagnosed hypertension and/or b. taking antihypertensive drugs. Hypercholesterolemia is defined by meeting either of these criteria: a. having a medical history of physician diagnosed hypercholesterolemia and/or b. the use of lipid-lowering medication. BMI is calculated by dividing the patients' weight in kilogram by the square of their height in meters at the time of iSSNHL diagnosis. Smoking status is recorded as either former,

current or non-smoker. Diabetes is defined by either having a medical history of physician diagnosed diabetes mellitus and/or the use of oral hypoglycemic drugs or insulin.

Aditionally, to account for potential confounding factors, binary and multinomial logistic regression analyses will be performed to compare the primary and secondary outcomes between both cohorts.

Treatment modalities

Corticosteroid therapy

The standard treatment for patients with iSSNHL is an oral corticosteroid regimen, consisting of 1mg/kg/day of prednisolone with a maximum of 60mg, administered for a period of 7 up to 14 days, Subsequently, the dosage is gradually reduced to zero over the same timeframe[24]. In case of a contraindication for oral corticosteroid use, intratympanic corticosteroid therapy is recommended. A 0.4ml to 0.8ml injection of either dexamethasone (10mg/ml) or methylprednisolone (30 to 40mg/ml) is injected into the middle ear every 3 to 7 days, for a maximum of 4 sessions. If no significant improvement in hearing is observed following oral corticosteroid therapy, intratympanic corticosteroid injection can be considered for salvage therapy.

Study procedures:

Subject identification and inclusion

Patients eligible for the study cohort will be recruited by their respective Ear, Nose and Throat (ENT) surgeons at participating centres. Patients eligible for the control cohort will be recruited by neurologists or ENT-surgeons at Gelre Hospital and ENT-surgeons in Leiden University Medical Center.

Data collection

Informed consent will be obtained during a telephone interview conducted several days after the patient receives the written patient information about the study. During this telephone interview, the patient will sign the informed consent form and return it to the research team at Gelre Hospitals, through postal mail. The interview will also include the identification of the patient's symptoms at the onset of iSSNHL, verification of their medical history and medication use.

Once the signed informed consent form is received by the coordinating investigator, relevant data from the participating hospitals will be sought. This data includes the patient's age, weight, height, medical history, current medication uses and their most recent MRI scan. For the SSNHL cohort, results from pure tone audiometric tests conducted before and after corticosteroid therapy, as well as results from video-head impulse testing and/or calorimetric tests, if performed, will be gathered. Additionally, details regarding the received treatment strategy will be collected.

MRI assessment

MRI scans will be included in the study if they were performed within six months prior to the onsef of sudden deafness or within 6 months afterwards. In order to be adequately analysed, the MRI requires either a T2 or FLAIR sequence of the entire brain. While an MRI of the cerebellopontine angle or entire brain is part of regular diagnostic work-up, the scanning protocol might vary somewhat between participating centres. The scanning protocol including types of sequences used, TR times, TE times, Voxel size, rotation and slice thickness for each patients will be documented upon finalisation of the study. Susceptibility weighted imaging is commonly included in the scanning protocol of the MRI's included in our study. The main limitation thereof is included in the limitation section.

The MRI scans retrieved will be assessed by 2 neuroradiologist separately, each with multiple years of experience in MRI assessment of head and neck pathology. The radiologists will be blinded for clinical data.. Figure 2 shows the scoring sheet used for MRI assessment. In case the degree of white matter hyperintensities differs 2 or more points on the Fazekas scale, the radiologist will review the MRI together until consensus is reached. Previous MRI assessments performed by both radiologists involved in this study demonstrated substantial interrater agreement in white matter hyperintensity assessment using the Fazekas score, with a kappa value of 0.74[20].

Ethics and dissemination

The Medical Research Involving Human Subjects Act does not apply to this study, as has been declared by the regional review board at Leiden University Hospital, registration number 22-3060. Ethical approval for participation has been obtained by the institutional review boards of participating hospitals prior to the start of inclusion in these centres. The study received the following registration numbers according to participating centre: Leiden University Hospital: 22-3060; Gelre Hospitals: 2022.47 ; Groene Hart Hospital: LI-2023-05; Isala Hospital: 20230413; Medisch spectrum Twente: KH23-23; Rijnstate hospital: 2023-2207; Treant Emmen:2023-16, St. Franciscus 2022_47, Rivierenland Tiel 22-3060.

The final results of the study are planned to be published in an open access journal after completion of analyses. For information regarding deposition of data, see the separate section.

Informed consent

Prior to seeking consent to enter the study, participants will receive an explanation of the study along with an information leaflet, followed by a minimum of 5 days for consideration. Participants have the right to decline participation without the need to provide a specific reason. If patients do

not give consent in participating in the study, their contact information will thereafter be deleted from our records.

Data handling

Personal data, including medical history and diagnostic test results, will be sent to the investigating site via digitally protected email, after informed consent has been obtained.

Upon arrival at Gelre Hospital, the relevant information will be extracted from the received files. Subsequently, this data will be pseudonymized and stored in a research database, using Castor EDC (Castor EDC, Amsterdam, The Netherlands). The original files will be stored on a protected data drive at the ADC.

MRI scans obtained from participating hospitals will be shared electronically via the national Twiin platform for data exchange, developed by Vereniging van Zorgaanbieders voor Zorgcommunicatie (VZVZ), Den Haag, The Netherlands. The MRI scans will be pseudonymised and uploaded to a secured Picture Archiving and Communication System (PACS) worklist at the radiology department of Gelre Hospital Apeldoorn. Following assessment of the pseudonymised MRI-scans, this PACS worklist will be deleted, while the MRI scans themselves have been stored on a protected data drive of the ADC.

The assembled document files, digital files and MRI-scans will be saved for a period of 15 years on a protected data drive at the ADC. When this period has passed, all data will be deleted and all files will be destroyed.

Risks and benefits

Participants in this study will not be subjected to any additional study-related interventions beyond standard medical practices, such as MRI scans and audiometric testing, which are typically performed

when SSNHL is suspected. No blood investigations or procedures beyond the established iSSNHL treatment guidelines in the Netherlands will be included in this study.

Implications for future research

The identification of vascular involvement in the onset of sudden deafness could have serious implications for the current treatment guideline of sudden hearing loss. Specifically, for a subset of patients that appears to have increased cardiovascular comorbidity, consideration of cardiovascular risk management, including anticoagulant administration, could be warranted. If the results of the cross-sectional study, as described in this paper, provide evidence for vascular involvement in the pathophysiology of sudden sensorineural hearing loss, follow-up investigation of the included study population could be beneficial. This follow-up could imply a retrospective investigation of the incidence of stroke in the five years after inclusion in this study.

Data deposition

Upon reasonable request, the dataset and statistical code may be shared by contacting the primary author. The dataset will not be publicly accessible. To stimulate transparency and improve future research, this protocol will be published open access.

Patient and public involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

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Tables

Inclusion criteria sudden deafness cohort	*Inclusion criteria control cohort*

• Sudden deafness defined by acute onset sensorineural hearing loss of at least 30dB on 3 consecutive frequencies occurring withing 72 hours or less. • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years	• Patients diagnosed with trigeminal neuralgia, hemifacial spasm, vestibular paroxysmia or a cerebellopontine neoplasm. • Absence of sudden sensorineural hearing loss • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years
Exclusion criteria	
• Diagnosis of sudden deafness prior to the study period. • Significant cerebral damage due to a pre-existing medical condition that will impede an adequate assessment of the degree of cerebral small vessel disease. For instance, a medical history of multiple sclerosis. • Presence of an enlarged vestibular aqueduct on MRI that could be responsible for SSNHL • An identifiable cause of iSSNHL such as a Borrelia Burgdorferi infection.	

Table 1. Inclusion and exclusion criteria for participation in the ROSALIE study. FLAIR=fluid attenuated inversion recovery, iSSNHL=idiopathic sudden sensorineural hearing loss.

Figure legends

Figure 1. The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

Figure 2. MRI assessment sheet. The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

Authors contributions

All authors have contributed to the study design. F. Oussoren, R.B. van Leeuwen, M. Lammers and T.D. Bruintjes are responsible for the overall conduct of the study. T. Bruintjes is the guarantor of this study. C. Colijn and F. Oussoren will be responsible for the data collection. F. Oussoren and T. Schermer will be responsible for the statistical analysis. J. Kardux and L. Poulsen will be responsible for the MRI assessment. E. Hensen will be responsible for the inclusion of the control cohort.

MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test for Ordered Categories

		1		
	Test Significance Level, a	0.050		
	1 or 2 Sided Test?	2		
	Number of Categories, k	7		
	Side Table Name	MTT2S-1		
	p1 P(X<Y)			
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	Sample Size per Group, n	205		

MTT2S-1

Σ Compute ↕ Transfer X Clear

	Category	Proportion in Controls (X)	Proportion in SSNHL (Y)
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1. Fazekas score

A. periventricular white matter (PVWM)	
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2. Silent brain infarctions*

	Yes= 1 / No= 0	Remarks
Presence		
Size (in mm)		

*SBI’s need to meet the following criteria:

1. Minimal size of 3mm
2. Cerebrospinal fluid (CSF) appearance in all MRI sequences.
3. Can be differentiated from dilated Virchow-Robin spaces (dVRS)