University College London

Faculty of Brain Sciences

Ear Institute

Clinical and imaging biomarkers of audiovestibular function in infratentorial superficial siderosis

A Thesis Presented for the Degree of

Doctor of Philosophy

by

Natallia Kharytaniuk

23RD October 2022

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DECLARATION

I, Natallia Kharytaniuk, confirm that the work presented in this thesis is my own. I confirm that where the information derived from other sources has been included in my thesis, this has been indicated in my thesis, and such sources are acknowledged accordingly. All studies conducted as part of this thesis were undertaken following the approval of the National Health Service Health Research Agency and Health and Care Research Wales Research Ethics Committee, the University College London Research Ethics Committee, and the clinical governance teams at the National Hospital for Neurology and Neurosurgery and the Royal National ENT and Eastman Dental Hospitals at the University College London Hospitals NHS Foundation Trust. The research studies were carried out in accordance with the principles of the Declaration of Helsinki. All individuals participating in the research studies gave informed consent prior to their participation.

This work was undertaken under the supervision of Professor Doris-Eva Bamiou, Professor David John Werring and Professor Anne Schilder at the University College London Ear Institute and the Queen Square Institute of Neurology, and the Neuro-otology Department at the Royal National Ear Nose and Throat and Eastman Dental Hospital, University College London Hospitals NHS Foundation Trust. This work was funded by the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre Deafness and Hearing Problems Theme (doctoral studentship programme number BRC-1215-20016-546624-175870). Additional funding for part of the project was received from the Bernice Bibby Research Trust, and Health Utilities Index Inc (licence fee waiver). The study on the prevalence of iSS in a UK population sample was conducted using the UK

Biobank Resource under Application Number 16256. Pilot findings from the research study presented in Chapter 6 (QoL in iSS and ARHL study) were submitted by student Amir Ala Mazaheri for the award of Master of Science Degree at Queen Square Institute of Neurology, University College London (September 2020).

Signature

Date: 23rd of October 2022

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I am grateful to my parents who instilled in me love for music since young age. It is through my love of music that I appreciate the importance of hearing, and I am delighted to have been part of the research into hearing loss to tackle this growing problem. I would like to say my biggest 'thank you' to all my family and all my friends, near and far. For your tremendous support and encouragement throughout my studies and beyond, for picking me up during my lows and for sharing my highs. From the bottom of my heart – thank you.

ABSTRACT

Disabling hearing loss is known to affect over 400 million people worldwide while the lifetime prevalence of dizziness can be as high as 40%. Rare causes for hearing and balance impairment are often understudied. Infratentorial (classical) superficial siderosis (iSS) is a rare but sometimes disabling complex neurological condition most often associated with hearing and balance impairment, and myelopathy. Olfactory loss has been reported but not yet systematically studied. iSS results from a chronic low-grade and low volume bleeding into the cerebrospinal fluid and the deposition of iron-degradation products (predominantly haemosiderin) in the subpial layers of the central nervous system, with predilection for the cerebellum and the vestibulocochlear nerves. Magnetic resonance imaging (MRI) allows haemosiderin to be visualised in-vivo and is the mainstream diagnostic modality. Due to the assumed rarity of iSS (prevalence of 0.03-0.14%), our research opportunities are limited. Few dedicated studies describe iSS-related audiovestibular (AV) findings, often limited to case-series, with mixed findings. There is currently no robust evidence that the radiological haemosiderin appearances correlate with the objective clinical tests.

This project focuses on phenotyping the AV function in iSS and identifies predominantly retrocochlear hearing loss with features suggestive of central auditory dysfunction, and mixed vestibular (predominantly cerebellar) dysfunction. This work introduces and validates an imaging rating scale aiming to capture the anatomical extent of haemosiderin deposits visualised on MRI in a standardised and reproducible way. The scale demonstrates excellent reliability and good validity, with the scores correlating with hearing thresholds. This project estimates the prevalence of MRI-defined iSS in a large UK Biobank sample, similar to other rare neuro-

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otological disorders. Using patient/self-report measures, this work captures markedly low health-states of individuals with iSS and identifies possible iSS-specific auditory characteristics. Finally, the work identifies high prevalence of olfactory dysfunction in individuals with iSS.

IMPACT STATEMENT

The overarching theme of this work is infratentorial superficial siderosis – a rare neurological condition on which our clinical knowledge and research opportunities are limited. For over a century, since its first description in 1908, our knowledge has expanded through dedicated work which has led to our understanding of the underlying pathophysiological processes, improved our knowledge of the key clinical and diagnostic features of iSS, and initiation of possible treatment strategies. Despite this, many knowledge gaps remain and the opportunities for research are still limited.

This work builds on the current knowledge on iSS, with the primary focus on the hearing and balance impairments which are the common features of iSS and expands our knowledge of the iSS-related radiological features. This work brings into focus the iSS-related audiovestibular and radiological features and describes novel findings on iSS prevalence in the UK and the impact of iSS on health-related quality of life of individuals with this disorder. The strength of this work is its size of the study cohorts which can be considered large in comparison to other studies on iSS published to date.

The identification of common audiovestibular features in individuals with iSS can help clinicians to refine their assessment of such patients, help reach correct and timely diagnosis and propose a management plan that can better address the patients' functional needs. This work highlights the importance of using the already available instruments and also introduces new tools for assessment of such patients in the clinical setting and proposes the use of these tools in future research studies.

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The new findings of iSS prevalence in the general UK population and the findings of the impact of iSS on the overall health-related quality of life are important as they highlight the need for resource allocation in the clinical and research settings to meet the needs of patients and to provide opportunities for further research in this area.

This work may help to further raise awareness and improve our understanding of iSS. It may be relevant for clinicians, policy makers, and researchers, and provides direction for future research in this area including, ultimately, clinical trials.

RESEARCH PAPER DECLARATION FORMS

The findings (including three figures) from the following published papers have been included in this thesis, with the permissions obtained from the publisher where necessary, and are acknowledged and referenced accordingly.

1. Health-Related Quality of Life in Adults With Classical Infratentorial Superficial Siderosis: A Cross-sectional Study. N Kharytaniuk, et al (*Neurology,* 2022)

2. Olfactory dysfunction is common in classical infratentorial superficial siderosis of the central nervous system. N Kharytaniuk, et al (*Journal of Neurology,* 2022).

3. Classical infratentorial superficial siderosis of the central nervous system: pathophysiology, clinical features and management. N Kharytaniuk, et al (*Practical Neurology,* 2022).

4. Case report: auditory neuropathy and central auditory processing deficits in a neuro-otological case-study of infratentorial superficial siderosis. N Kharytaniuk, et al. (*Frontiers in Neurology,* 2021).

5. *Neuropsychological and neuroimaging characteristics of classical superficial siderosis.* E Chan, et al (*Journal of Neurology,* 2021).

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PUBLICATIONS AND PRESENTATIONS RELATED TO THIS WORK

Publications

<u>Published</u>

1. *Health-Related Quality of Life in Adults With Classical Infratentorial Superficial Siderosis: A Cross-sectional Study*

   N Kharytaniuk, AA Mazaheri, M Pavlou, DJ Werring, DE Bamiou. ***Neurology.*** 2022 Aug 25. doi: 10.1212/WNL.0000000000201115 (published online ahead of print).

2. *Olfactory dysfunction is common in classical infratentorial superficial siderosis of the central nervous system*

   N Kharytaniuk, EA Lim, E Chan, M Pavlou, DJ Werring, DE Bamiou. ***Journal of Neurology*** (published 23rd August 2022) doi 10.1007/s00415-022-11329-y

3. *Classical infratentorial superficial siderosis of the central nervous system: pathophysiology, clinical features and management*

   N Kharytaniuk, P Cowley, P Sayal, P Eleftheriou, SF Farmer, E Chan, DE Bamiou, DJ Werring. ***Practical Neurology*** 2022;22:274-284.

4. *Case report: auditory neuropathy and central auditory processing deficits in a neuro-otological case-study of infratentorial superficial siderosis*

   N Kharytaniuk, P Cowley, DJ Werring, DE Bamiou. ***Frontiers in Neurology*** 2021, Jan 14;11:610819. Doi: 10.3389/fneur.2020.610819.

5. *Neuropsychological and neuroimaging characteristics of classical superficial siderosis*

   E Chan, Y Sammaraiee, G Banerjee, AF Martin, SF Farmer, P Cowley, P Sayal,

N Kharytaniuk, P Eleftheriou, J Porter, N van Harskamp, L Cipolotti, DJ Werring.

Journal of Neurology 2021, Nov;268(11):4238-4247. Doi: 10.1007/s00415-021-10548-z. Epub 2021 Apr 17.

6. *Targeted detection and repair of a spinal dural defect associated with successful biochemical resolution of subarachnoid bleeding in classical infratentorial superficial siderosis*

R Lobo, B Batbayar, **N Kharytaniuk,** P Cowley, P Sayal, SF Farmer, DJ Werring.

Neurological Sciences 2022.Jun;43,5643-5646. Doi.10.1007/s10072-022-06181-x.

Presentations

<u>Poster presentations</u>

1. *Quality of life in classical (infratentorial) superficial siderosis*

   N Kharytaniuk, AA Mazaheri, M Pavlou, DJ Werring, DE Bamiou

   Association of Research in Otolaryngology 45TH Annual Mid-Winter Meeting, January 5 -9th, 2022, San Jose, CA, USA –poster presentation (virtual)

2. *Olfactory function in classical (infratentorial) superficial siderosis*

   N Kharytaniuk, AA Mazaheri, M Pavlou, DJ Werring, DE Bamiou

   Association of Research in Otolaryngology 45TH Annual Mid-Winter Meeting, January 5 -9th, 2022, San Jose, CA, USA –poster presentation (virtual)

3. *Audiovestibular findings in infratentorial classical superficial siderosis*

   N Kharytaniuk, D Wilson, G Banerjee, SF Farmer, P Cowley, DJ Werring*, DE Bamiou*

   American Academy of Audiology and Tech EXPO 2020, April 1-4th, 2020, New

Orleans, LA, USA – poster presentation (virtual); (*shared authorship) – poster selected as one of 10 nominees for the American Academy of Audiology Foundation's James and Susan Jerger Awards for Excellence in Student Research

<u>Podium presentations</u>

1. *Audiovestibular dysfunction in infratentorial (classical) superficial siderosis: retrospective cross-sectional study*

   N Kharytaniuk, D Wilson, G Banerjee, SF Farmer, P Cowley, DJ Werring*, DE Bamiou*

   Association of Research in Otolaryngology 43rd Annual Mid-Winter Meeting, January 25 -29th, 2020, San Jose, CA, USA – podium presentation, (*shared authorship

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LIST OF FIGURES

ABBREVIATIONS

ABR Auditory brainstem responses

AICA Anterior inferior cerebellar artery

ALS Amyotrophic lateral sclerosis

AN Auditory nerve

AP Auditory processing

APD Auditory processing disorder

ART Acoustic reflex thresholds

ASHA American speech and hearing association

BM Basilar membrane

BRC Biomedical Research Centre

BSA British Society of Audiology

CANS Central auditory nervous system

CANVAS Cerebellar ataxia with neuropathy and vestibular areflexia syndrome

CAPD Central auditory processing disorders

CCM Cerebral cavernous malformation syndrome

CI Confidence interval

CMT Charcot-Marie-Tooth disease

CN Cochlear nucleus

CNS Central nervous system

CP Canal paresis

CSs Corrective saccades

cSS Cortical superficial siderosis

CT Computerised tomography

CTM Computerised tomography myelogram

cVEMP(s) Cervical vestibular evoked myogenic potential(s)

daPa deka Pascal

dB Decibel

DICOM Digital imaging and communications in medicine

DP Directional preponderance

DPOAE(s) Distortion product otoacoustic emission(s)

ECoG Electrocochleography

ENG Electronystagmography

EQ5D EuroQOL-5D

ERSA Evaluation du Retentissement de la Surdité chez l'Adulte

FM Frequency modulated

fMRI Functional magnetic resonance Imaging

FRDA Friedreich's ataxia

GIN Gaps in noise

HG Heschel's gyrus

HHIE Hearing handicap inventory for elderly

HRQoL Health-related quality of life

HUI3 Health Utilities Index Mark III

Hz Hertz

IAA Internal auditory artery

IC Inferior colliculus

ICH Intracranial haemorrhage

IQ Intelligence quotient

iSS infratentorial superficial siderosis

LARP Left anterior right posterior

LL Lateral lemniscus

mAIADH modified Amsterdam inventory for auditory disability and handicap

MCA Middle cerebellar artery

MGB Medial geniculate body

MRI Magnetic resonance Imaging

Msec millisecond

NIFTI Neuroimaging informatics technology initiative

NHS National Health Service

NHNN National Hospital for Neurology and Neurosurgery

OAE(s) Otoacoustic emission(s)

oVEMP(s) Ocular vestibular evoked myogenic potential(s)

PTA Pure-tone audiometry

QoL Quality of life

QS Queen Square

RALP Right anterior left posterior

SCA Spinocerebellar ataxia

SCC Semicircular canal

SD Standard deviation

Sec Second

SIB Speech in babble

SIN Speech in noise

SL Sound level

SNHL Sensorineural hearing loss

SNR Signal-to-noise ratio

SOC Superior olivary complex

SPL Sound pressure level

SPV Slow phase velocity

SSQ Speech, spatial and qualities of hearing scale

SWI Susceptibility-weighted imaging

TC Time constant

TEOAE(s) Transient evoked otoacoustic emission(s)

TYMP Tympanometry

VAS Visual analogue scale

VFI Visual fixation index

vHIT Video head impulse test

VOR Vestibulo-ocular reflex

UCLH University College London Hospitals

CHAPTER 1   INTRODUCTION

1.1   Conflict of interest

This work was conducted as part of the University College London Ear Institute

Doctor of Philosophy (PhD) post-graduate research programme and was funded by

the National Institute for Health and Care Research University College London

Hospitals Biomedical Research Centre (Grant number BRC-1215-20016-546624-

175870). Additional funding for part of this project was obtained from the Bernice

Bibby Research Trust (England Registered Charity Number 1058703). Fee waiver

for the licence to use Health Utilities Index (Mark III) was sought for and granted from

Health Utilities Index Inc (Ontario, Canada). Pilot findings from the research study

presented in Chapter 6 (QoL in iSS and ARHL study) were submitted by student

Amir Ala Mazaheri for the award of Master of Science Degree at Queen Square

Institute of Neurology, University College London (September 2020). The data for

the study on the prevalence of iSS in a UK population sample was provided by the

UK Biobank Resource under Application Number 16256. Otherwise, no conflict of

interest exists with regards to this work.

1.2   Impact of COVID19 on this project

At the outset, the focus of this project was the prospective clinical research study

titled Audiovestibular Function in Infratentorial Superficial Siderosis (AViSS). It was

envisaged at the time that the AViSS study would include three participant groups,

one with the known diagnosis of infratentorial superficial siderosis (iSS, Type 1

classical), the second group would include participants with confirmed age-related

hearing loss (ARHL), and the third group would include participants without ARHL,

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i.e., with normal hearing. It was estimated that the project would include approximately 30 participants for each group, totalling 90 participants, and would span over a 2- or 3-year period. Following a consultation with a statistician, formal sample size calculation was deemed not necessary for the study in view of the rarity of iSS.

It was anticipated that the participants from all three groups would undergo the same auditory assessments to determine the salient auditory features for each group with the aim to distinguish iSS-related hearing loss from ARHL and normal-hearing individuals based on the audiological findings. In addition, the iSS group would undergo vestibular assessments to phenotype the iSS-related vestibular function. Due to rarity of iSS, it was also planned to collect venous blood samples for DNA analysis (which was subsequently amended to collect saliva samples instead, following the amendment approval by the NHS Research Ethics Committee). The NHS Research Ethics Committee approval for AViSS (including the amendment) was granted on the 6th of February 2020. Subsequently, after the beginning of COVID-19 pandemic, the recruitment and face-to-face participation of individuals in the research project were halted due to: (1) the national lockdown and (2) working restrictions, in line with the advice by the Public Health England to work from home; (3) the resultant closure of the testing facilities (4) the majority of potential participants being in the age-group deemed at a higher health-risk than the general population, and (5) some in the vulnerable category, and therefore needed to shield.

To mitigate these circumstances, the research project was adjusted. Several additional projects were put together so that the majority of the work on the project could be undertaken remotely.

Following the easing of the restrictions regarding the national lockdown, COVID-19 related amendments to the study were needed and were submitted to the UCLH/UCL Joint Research Office, on the advice from the NHS Research Ethics Committee. The amendments included: 1) provision of masks and gloves for the AViSS study participants travelling to and from the testing facilities, 2) provision of travel arrangements to and from the testing facilities such that to minimise the participants' risk from travelling in public transport with the strong preference for the travel by taxi or private car, and 3) shortening of the participants' length and number of visits to the testing facilities (achieved by performing the minimum necessary and clinically relevant audiovestibular testing), and the distribution and completion of self-administered tests remotely either electronically or by post. Smell identification test kits were distributed by post. It was decided not to collect saliva samples from the AViSS research participants.

Between November 2020 and July 2021, 17 consecutive patients with known diagnosis of iSS and under the clinical care of the specialist Superficial Siderosis multidisciplinary team at the National Hospital for Neurology and Neurosurgery, Queen Square (University College London Hospitals NHS Foundation Trust) were informed about the study taking place. Eleven of them expressed interest to participate in the AViSS study and were recruited to the study. No participants for other groups were recruited. Due to the time constrains and the funding allocated for

this doctoral research project, it was not possible to extend the duration of the AViSS study, including the recruitment times. The AViSS study was closed on 19/10/2021.

1.3   Overview

One in six people in the UK, and over 400 million people worldwide have disabling hearing loss, and the figures are predicted to double by 2050 (1). Unaddressed hearing loss has a great financial burden and a significant impact on the individual's personal and social life, with the most recent World Report on Hearing highlighting the need for clinical solutions to improve the lives of individuals with hearing loss (1, 2). Similarly, the prevalence of imbalance and dizziness in the general working and aged populations is high, with the lifetime prevalence of up to 40%, and is known to significantly impact the person's life and has a significant healthcare and socioeconomic burden (3-5).

Hearing loss and imbalance due to rare aetiologies may be understudied as research opportunities may be limited by low prevalence or access to dedicated specialist centres where research is likely to take place. Classical infratentorial superficial siderosis (iSS), also known as "superficial siderosis of the central nervous system" (CNS) is one such entity.

1.4   Current clinical knowledge

iSS is considered to be a rare neurological condition which develops as a result of chronic intermittent or continuous low volume bleeding into the cerebrospinal fluid (CSF) – often from a dural defect – and the deposition of iron degradation products (mainly in the form of haemosiderin) in the subpial layers of the structures of the

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(CNS). This leads to neuronal loss, gliosis and demyelination (6-8). Its onset is most often insidious, with protracted course, leading to slow and, probably, irreversible functional decline (8, 9). The diagnosis is often reached in the second half of life although iSS can affect individuals at any age (8). Significant morbidity may be established by the time of the diagnosis.

1.4.1 Clinical features associated with iSS

The most common clinical features of iSS are hearing loss, imbalance and ataxia, likely due to the involvement of the cerebellum, the brainstem and vestibulocochlear nerves (CNVIII) (8). Of those, hearing loss is most frequent (up to 95%) followed by ataxia and imbalance (88%) (8). Myelopathy is considered to be another core clinical feature of iSS and the presence of all three features constitutes the iSS clinical triad. Several other clinical features have also been described albeit less frequently which include olfactory and cognitive dysfunctions, sphincter disturbances, dysphagia and slurring of speech, seizures and some others (8, 10-14).

1.4.1.1 Audiovestibular function in iSS

The audiovestibular function in iSS can be assessed using validated and well-established tests in the clinical practices of audiology, audiovestibular medicine, neuro-otology and Ear, Nose and Throat (ENT) specialties. Each test assesses the function of a specific segment along the auditory and vestibular pathways. By combining the tests, attempts can be made to localise the affected segment along the pathway. The relevant anatomy is described below.

1.4.1.1.1 Overview of the auditory pathway and function

The auditory pathway can be divided into peripheral and central components. Anatomically, the ear is divided into external, middle and inner ear. External and middle ear are responsible for the conduction of sound waves to the inner ear, and the pathology affecting sound conduction can contribute to conductive hearing loss (15).

The inner ear houses cochlea which contains the Organ of Corti with outer and inner hair cells. They synapse with the distal segment of the auditory nerve via spiral ganglion. All of these structures are considered part of the peripheral auditory system (16).

Although peripheral hearing loss is often described with respect to cochlear versus retrocochlear involvement, retrocochlear involvement may imply either peripheral neural or central auditory involvement or both. "Cochlear" (or "sensory") hearing loss originates within cochlea and "neural" peripheral originating within the neural synapses or the auditory nerve (17, 18).

Involvement of the components of the central auditory pathway can result in central hearing loss. The central auditory system involves proximal part of the auditory nerve, the auditory nuclei within the brainstem, their neuronal projections to the auditory cortices and the primary, secondary and tertiary auditory cortices which include Sylvian fissures, insulae and Heschl's gyri, located in the superior temporal lobes (19).

1.4.1.1.2 Overview of the vestibular pathway and function

Similar to the auditory system, the vestibular pathway can be subdivided into peripheral (the end-organ and the vestibular nerves) and central components. The vestibular end-organ is known as the labyrinth and is housed in the inner ear next to the cochlea. It has five components which include three semicircular canals (anterior, lateral and posterior, also known as superior, horizontal and inferior, respectively) and the saccule and utricle (20). The semicircular canals (SCCs) detect angular head acceleration whereas the saccule and utricle detect linear and gravitational acceleration and deceleration (21).

The vestibular end-organs are innervated by two divisions of the vestibular nerve. The superior (segment of the) vestibular nerve synapses with the utricle, the lateral and anterior SCCs whereas the inferior (segment of the) vestibular nerve synapses with the saccule and the posterior SCC on each side (22, 23). Both (superior and inferior) vestibular nerves are located in the posterior part of the vestibulocochlear nerve bundle in the internal acoustic canal whereas the auditory (cochlear) nerve and the facial nerve are located antero-inferiorly and antero-superiorly, respectively (22, 23).

The vestibular end organs and the superior and inferior vestibular nerves constitute peripheral vestibular pathway. The nerves synapse with the second order neurons in the Scarpa's ganglion from where the central vestibular pathway commences (24). The second-order neurons project to the brainstem nuclei; from there, third order neurons project to the five structures and organs: thalamo-cortical nuclei, cerebellum, oculomotor nuclei, spinal cord and the autonomic centres within the

medulla (21, 23). The complex neuronal network between these structures
coordinates head, eye and body movements (23).

The connection between the vestibular and oculomotor nuclei is responsible for the
oculomotor function and the vestibulo-ocular reflex which ensure steady visual input
(gaze stabilisation) during the head and body movements (20). The response of
vestibulo-ocular reflex is directly opposite to that of the head movements (23, 25).
The following eye movements are part of the oculomotor function: saccadic eye
movement, optokinetic nystagmus and smooth pursuit. Saccadic eye movement is a
fast velocity eye movement that allows the eyes to quickly focus on different objects
of interest after a rapid change of direction (refixation) (21). Optokinetic nystagmus is
a slow velocity tracking system that allows the gaze to be stable while the
surroundings are moving (25). Smooth pursuit allows the individual to maintain a
sharp focus when tracking a moving object while the head is stationary (21). The
simultaneous movement of the eyes and head – as when following a moving object –
can be achieved by suppressing the vestibulo-ocular reflex (fixation) (21).
Therefore, recording of the eye movements as a means to assess the individual's
oculomotor function and the vestibulo-ocular reflex and the ability to suppress it
forms the basis for several clinical vestibular tests and can be used to help
differentiate between central and peripheral vestibular lesions (26).

1.4.1.1.3 Reports of iSS-related audiovestibular function

Despite hearing loss and imbalance being the most common features of iSS, few
reports exist in the scientific literature that describe the audiovestibular findings in
individuals with classical iSS, and the reports of detailed audiovestibular findings are

even fewer. In the majority, these are single case reports or case series, with the

cohort numbers predominantly in single or teen figures (27).

Overall, the reports describe mixed central (cerebellar or other structures of the

central vestibular pathway) and peripheral vestibular involvement, and cochlear and

retrocochlear involvement of the auditory pathway. To date there have been no

dedicated reports describing non-cerebellar central vestibular function in iSS.

1.4.1.1.3.1 *Auditory function in iSS*

Hearing loss is the most commonly reported feature of iSS (8). The auditory function

in iSS has been assessed using a variety of tests which can vary between the

studies. In addition to pure-tone audiometry assessments (PTA) some studies also

include the findings from the auditory brainstem evoked response testing (ABRs)

(28-35), speech audiometry (29, 32, 36-38), acoustic reflex testing (ART) (30, 39).

Other studies report the findings from the otoacoustic emissions (OAE) and

electrocochleography (ECoG) testing (30, 31, 33, 37, 38, 40).

Overall, the majority of reports characterise iSS-related hearing loss as bilateral

sensorineural often asymmetric and of variable degree. Sparing of lower frequencies

has been described in the early stages of the disease with the characteristic

"downsloping" configuration on PTA. Flattening of the configuration of the thresholds

can occur with further involvement of mid- and low-frequencies, likely in the setting of

disease progression (8, 13, 41, 42). The downsloping configuration of thresholds in

iSS may resemble that of ARHL. There have been reports of individuals presenting

to healthcare facilities with iSS-related hearing difficulties which were attributed to

age and the patients re-presented later with more debilitating symptoms (13). Similar

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to the individuals with ARHL, iSS patients may present to the healthcare facilities with hearing problems in the second half of life and report hearing difficulties in the presence of background noise and may have tinnitus (13, 42-44). It is therefore important to describe the salient auditory features of iSS which could distinguish iSS-related hearing loss from ARHL. The onset of iSS-related hearing loss may however be earlier than in age-matched populations, and asymmetry in the thresholds may suggest aetiology other than ARHL (13, 43). However, no dedicated studies exist to date that assess the difference in the auditory features in individuals with iSS versus with ARHL.

The hearing loss in iSS is described of cochlear origin in some studies whereas other studies report retrocochlear origin. It is difficult, however, to ascertain the involvement of the exact segment of the auditory pathway. This is due to a variety of tests which have been used to assess the iSS-related auditory function described in the reports. An additional challenge when evaluating the iSS-related auditory dysfunction may be due to the severe or profound hearing loss in which cases it might not be possible to perform all the necessary tests to reliably ascertain the location of the affected segment of the auditory pathway.

The largest study to report auditory findings in iSS was a retrospective review of medical records of 49 patients with superficial siderosis of the CNS (13). Hearing loss and imbalance were reported in 92% and 67% of patients, respectively (13). The auditory function was assessed in 24/49 (49%) patients whereas 13/49 (37%) of the cohort underwent vestibular assessments. The study included PTA, word and speech recognition thresholds, and ART, and demonstrated mixed (cochlear and

retrocochlear) origin of the auditory dysfunction (13). The hearing loss was reported to be downsloping and asymmetric and exceeded the hearing loss expected for the patients' age. The patients demonstrated decreased speech recognition. Similar findings were observed in the group's subsequent prospective study (n=10) in which measurement of cochlear function with distortion product otoacoustic emissions (DPOAEs) was included (42). DPOAEs were also reported to be absent in 16/20 (80%) of ears (42). The participants, however, did not undergo ABR nor had formal vestibular assessment. The findings of speech audiometry can, where described, vary from normal speech recognition to reduced or poor (29, 30, 36, 37, 40, 42, 45-47). It has been suggested that the speech recognition may worsen with progression of the disease (29, 30, 33, 45).

Absent acoustic reflexes have been reported in some studies (8, 42). And absent OAE responses have also been reported (33, 37, 38). A case described by Takasaki et al, reported absent distortion product OAEs (DPOAEs) and electrocochleography (ECoG) responses, in addition to the elevated auditory thresholds (40). Absent ECoG responses were also reported by Irwin et al (31).

Where reported, ABR findings have also been described as variable, with abnormal or absent responses (31, 34, 37). Some studies reported prolonged wave I-V inter-peak latencies or prolonged Wave I-III inter-peak and normal Wave III-V latencies (28, 29, 34, 48). Normal ABR was reported in one patient (34). Ushio et al. reported asymmetrical sensorineural hearing loss (SNHL) of moderate to profound levels in one patient, with peaked Wave I only in the better hearing ear (49).

There have been no detailed studies assessing the function of the auditory cortex in individuals with iSS to date. It may, however, be affected as radiological findings consistent with haemosiderin deposits which have been reported on imaging and described to involve the cortical surfaces of key central auditory processing areas such as the temporal lobes, insulae and Sylvian fissures, as well as the brainstem (7). To date, central auditory processing deficits have not been studied or reported except in a single case report (43), as part of this work (50).

Based on the current evidence and due to the heterogeneity of the auditory reports available to date, it is difficult to determine the pattern of the auditory dysfunction in individuals with iSS, to locate the affected segment along the auditory pathway and to ascertain the pattern of progression of the iSS-related auditory dysfunction. Gaining a better understanding of the audiological profile in individuals with iSS may not only allow to identify the features differentiating iSS-related hearing loss from ARHL but also help to determine the usefulness of the current management strategies for hearing loss in this population as well as the likely benefits (or lack thereof) from conventional hearing aids and cochlear implants in such patients.

1.4.1.1.3.2 _Vestibular function in iSS_

The reports describing the balance function in iSS appear to be even fewer, compared to the volume (albeit small) of the audiological reports (27). Similarly, the vestibular test battery described to date does not appear to be uniform. While several studies report the findings of electronystagmography (ENG) (30, 34, 36, 46, 51), some also describe vestibular evoked myogenic potential (VEMP) testing (30, 47) and video head impulse testing (vHIT) (33, 52, 53). Of the peripheral vestibular

function reports, the common findings are reduced vestibulo-ocular reflexes (VOR), and absent VEMPs (47, 54-57).

The majority of the reports describe the vestibular involvement as mixed – of central (cerebellar or involving other structures of the central vestibular pathway) and peripheral (involving the vestibular nerves and the end organs) origin. However, similar to the reports on auditory findings, it is difficult to ascertain the exact segment of the vestibular pathway involved in iSS.

Yoo et al reported the presence of bilateral mixed cochleovestibular loss and suggested that VOR gain may potentially be reflective of the severity of vestibular impartment in iSS. The team proposed vHIT to be used routinely for vestibular assessment of patients with iSS (53).

Similarly, Kang et al reported reduced VOR gains on vHIT with abnormal saccades in all SCCs in a 60-year-old patient with severe gait disturbances and severe SNHL (52). The patient was diagnosed with bilateral peripheral vestibulopathy (without the central component) secondary to iSS (52).

Miwa et al reported vestibular findings in five patients with superficial siderosis (47). VEMP testing showed diminished or absent utricular/superior vestibular nerve function in all five patients, and a progressive deterioration in the saccular/inferior vestibular nerve function. The authors associated the changes with disease progression and concluded that the location of the lesion which would account for the patients' impaired balance was both in the central and the peripheral components of the vestibular pathway (47).

Ushio et al reported bilaterally absent VEMPs in a 64-year old male with the diagnosis of iSS and a 20-year history of progressive hearing loss and ataxia (49). Ice water responses and spontaneous nystagmus were absent on caloric testing.

Vibert et al reported findings from PTA, ABR and ENG of three patients with iSS which demonstrated moderate-to-profound SNHL, variable latencies on ABR associated with disease progression and mixed central (cerebellar) and peripheral vestibular deficits (34).

Kattah et al reviewed 57 patients with bilateral vestibular loss (56). Of those, three were found to have superficial siderosis and had bilateral mixed vestibular dysfunction with impaired dynamic visual acuity, abnormal v-HIT and absent or reduced caloric responses (56).

The largest study describing vestibular findings in individuals with iSS was by Takeda et al and included 10 patients who underwent electronystagmography, video head-impulse test and posturrography (58).

1.4.1.2 Myelopathy features

Myelopathy-related features are considered common in iSS and constitute part of the iSS clinical triad (8). These may include limb weakness, sensory disturbances, pain, spasticity, - most commonly in the lower limbs - as well as upgoing extensor plantar responses, hyperreflexia and pyramidal weakness (8). These may also contribute to the imbalance reported by patients with iSS.

1.4.1.3 Cognitive function

Cognitive impairment appears to be another feature of iSS. Reports of dementia in individuals with iSS had been previously described but this was not supported in a recent study by Chan et al (8, 12, 39, 59-61). Cognitive compromise was observed in up to 50% of the 16 individuals with iSS (12). The most common findings were the deficits in executive function, in non-verbal and verbal memory domains as well as speech production (12). The number of impaired cognitive domains and performance intelligence quotient (IQ) were correlated with disease duration.

1.4.1.4 Olfactory function

Olfactory dysfunction may also be a clinical feature of iSS and has been described in 13 to 44% of individuals with iSS (8, 9, 62, 63). Involvement of the olfactory nerve (CNI) has been described in histological reports (64). However, iSS-related olfactory dysfunction has not been formally studied to date.

1.4.1.5 Other features of iSS

Other features of iSS include sphincter disturbances and associated bladder and bowel voiding difficulties. Altered sensation during voiding as well as urinary or faecal incontinence, constipation or symptoms of neurogenic bladder have been described in patients with iSS (8, 9).

Presence of diplopia and vision disturbances, dysphagia or dysphonia which have been described in patients with iSS may signal the involvement of other cranial nerves (8). Pain from arachnoiditis or myelopathy may also be present in patients with iSS. In few cases, seizures have been described (8, 9).

1.4.2   Radiological diagnostic criteria and features

Up until the advent of magnetic resonance imaging (MRI), the diagnosis of iSS was made predominantly at autopsy or intraoperatively, or clinically in the presence of the triad of hearing loss, ataxia, myelopathy and the previous history of trauma or surgery to the CNS (8). The first radiological description of superficial siderosis dates back to 1985 and reports MR findings of the rims of hypo-intense areas along the surfaces of the brain, brainstem, and spinal cord (65). Since then, MRI has become the reference standard for diagnosing superficial siderosis as it allows in vivo visualisation of the haemosiderin deposits as well identifying the pattern of haemosiderin distribution. MRI is also the modality of choice to investigate ataxia and SNHL in patients with the suspicion of iSS (7, 8, 66, 67).

In the past few decades further advances in MRI techniques have allowed the introduction of paramagnetic sequences which are sensitive to iron such as T2* Gradient-Recalled Echo (T2*GRE) and an even more recently introduced susceptibility-weighted imaging (SWI). Although signal loss and the appearance of hypointense regions of iron-laden tissues or lesions can be observed on T2-weighted (as well as T2*GRE and SWI sequences), the haemosiderin regions are more conspicuous on iron-/paramagnetic-sensitive sequences than when visualised on T2-weighted MRI (68-70). This is due to the presence of associated "blooming effect" defined as the signal loss extending beyond the iron-containing tissues' (68-70). SWI has a greater contrast-to-noise ratio and spatial resolution than T2*GRE which allows for better visualisation of the tissues or lesions containing iron, including microhaemorrhages (71-73).

The radiological diagnostic criteria for iSS have been proposed by D Wilson, DJ Werring and their colleagues (7). The criteria are based on identifying a distinct and symmetrical pattern of haemosiderin distribution of the key infratentorial regions (7). According to the criteria, the MRI appearances of haemosiderin are considered diagnostic of iSS in the presence of a well-defined symmetrical homogenous signal loss along the superficial surfaces of at least two of the following CNS regions: cerebellum (including cerebellar folia, flocculus or peduncles), brainstem (including midbrain, pons or medulla), cranio-cervical junction or spinal cord (7) **(Figure 1.1).** Involvement of at least two of these structures constitutes the radiological criteria for iSS diagnosis (7).

The group also described, in addition to the infratentorial involvement, the findings of supratentorial haemosiderin distribution, however this was not considered a diagnostic feature (7). Supratentorially, the signal loss was observed over the surfaces of cerebral convexities of temporal, frontal, occipital, and parietal lobes, as well as interhemispheric and Sylvian fissures (7).

Haemosiderin deposits may also be visualised on MRI in a limited and asymmetrical distribution either infratentorially or supratentorially or both, often following a single haemorrhagic event (7).

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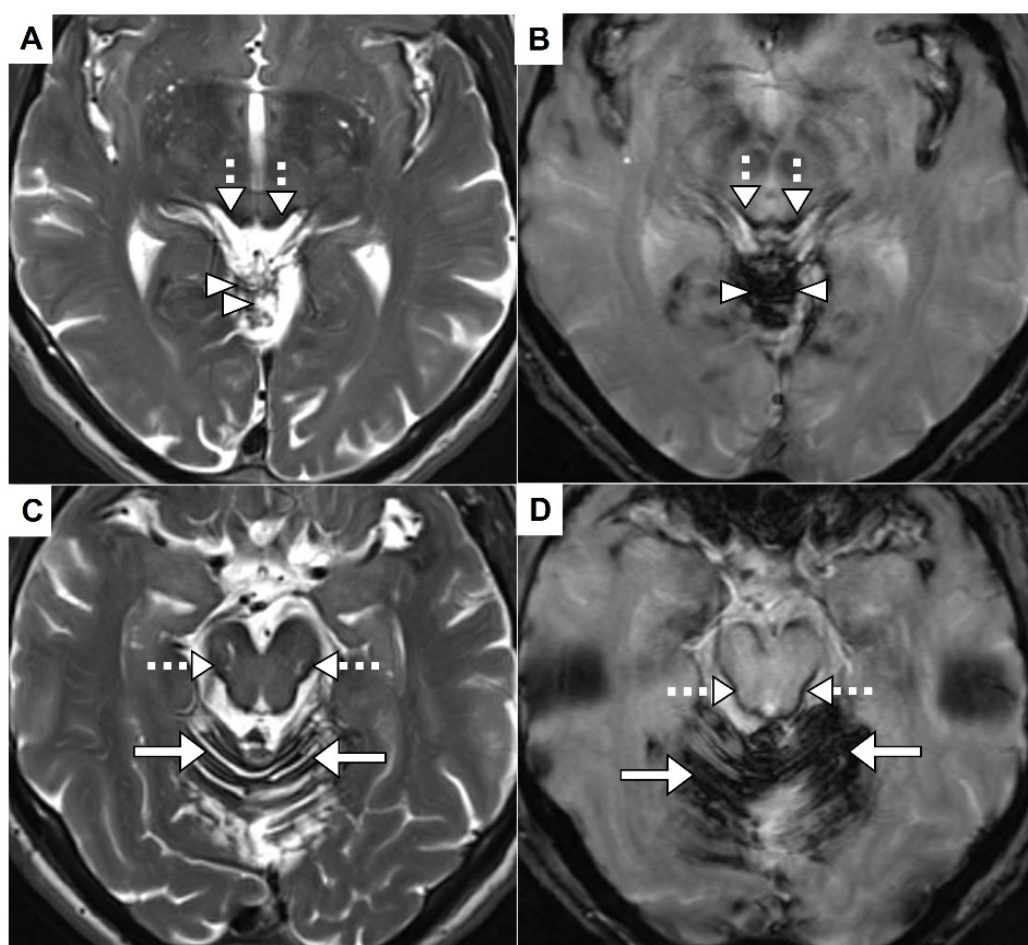
Figure 1.1. Axial T2-weighted (A, C) and corresponding susceptibility-weighted (B, D) MR images of haemosiderin appearances, demonstrating characteristic signal loss consistent with haemosiderin deposits involving superior vermis (arrowheads, A, B), cerebellar folia (solid arrows, C, D) and midbrain (dashed arrows, A-D). Figure reproduced under the Creative Commons CC-BY 4.0 International licence, from Kharytaniuk et al (Neurology, 2022) (74).

The introduction of the iSS radiological diagnostic criteria may help to standardise the description of haemosiderin distribution in cases with confirmed iSS diagnosis and rule out cases of superficial siderosis with limited or asymmetrical haemosiderin distribution. For example, in a case-series of audiovestibular findings in superficial siderosis, Miwa et al included findings from a case with siderosis in which the signal changes consistent with haemosiderin were observed to involve only the right temporal lobe and basal ganglia, and thus not fitting the radiological diagnostic

criteria for iSS (47). This is important not only for correct diagnosis but also in the research settings. Detailed and systematic description of MRI findings in individuals with iSS has not been performed to date.

In addition, it remains unclear whether visualisation of haemosiderin on MRI correlates with the clinical burden of the disease and the functional impairment in individuals with iSS and whether imaging can be used as a means to monitor disease progression or response to treatment. Attempts have been made to quantify haemosiderin deposits by using quantitative susceptibility mapping (QSM) which allows to quantitatively measure the magnetic susceptibility of tissues, or by measuring susceptibility-related signal change on interval imaging (75-78). These techniques however are currently available in the research but not clinical settings. A limited number of studies have also attempted to correlate the imaging findings with the clinical features of iSS (75, 76). Nose et al described the response to treatment in iSS by measuring haemosiderin load on imaging using susceptibility signal contrast ratio before and after the treatment and measuring ataxia using ataxia rating scales (76). In another study Kessler et al attempted to correlate the imaging findings with the participants' subjective reports of their perceived hearing function following the treatment. The team did not assess the auditory function by performing the auditory tests (75).

1.4.3 Classification and nomenclature of superficial siderosis

The first description of superficial siderosis was reported by Hamill in 1908 following a post-mortem examination. It was termed "melanosis" due to the darkened appearances of the surfaces of the affected CNS organs (79). Since then, several

terms for superficial siderosis have been proposed and used, often interchangeably. These include "siderosis (or haemosiderosis) of the CNS", "leptomeningeal" or "meningeal" or "subpial haemosiderosis" (9, 14, 80).

Up until recently, the term "superficial siderosis involving the CNS" has been used more commonly and referred to the clinical syndrome with the typical features of hearing loss, imbalance and ataxia, and myelopathy. The term may have also incorporated superficial siderosis involving cerebral cortical areas, with their appearances described as "tram-tracking" on paramagnetic MRI yet without the infratentorial involvement (7, 81, 82). This type of superficial siderosis of the CNS has since been termed cortical superficial siderosis (cSS) (82). cSS is a separate entity to iSS, with different clinical features, radiological findings and pathophysiological characteristics than of iSS (**Figure 1.2**) (7, 82). Both can, however, co-exist. cSS is more likely to be present in older individuals and it can be associated with cerebral amyloid angiopathy (7, 83, 84). In cSS, the haemosiderin distribution demonstrates supratentorial pattern – involving cerebral hemispheres – without the infratentorial involvement which may differentiate it from iSS. In contrast, the latter demonstrates invariable involvement of the infratentorial structures, with or without supratentorial involvement (82, 84, 85). Hearing impairment or symptoms of imbalance or ataxia are rarely reported in patients with cSS and are unlikely to be due to cSS but rather due to age-related changes or other co-morbidities (14).

Furthermore, two sub-types of iSS have recently been recognised (7). Type 1 (classical) iSS refers to the iSS with the characteristic clinical syndrome of hearing loss, ataxia and imbalance, and myelopathy which, as mentioned earlier, may

develop over time as a result of chronic continuous or intermittent extravasation of blood, and demonstrates symmetrical deposition of haemosiderin along the infratentorial structures (7). In contrast, Type 2 (secondary) iSS, is likely to occur as a result of a once-off bleeding event into the cerebrospinal fluid (CSF) such as an acute subarachnoid haemorrhage from an aneurysm or at the time of CNS surgery (7). The individuals with Type 2 iSS are unlikely to have the typical clinical syndrome associated with the classical (Type 1) iSS. For the purposes of this work, the term "iSS" refers to classical Type 1 iSS, unless specified.
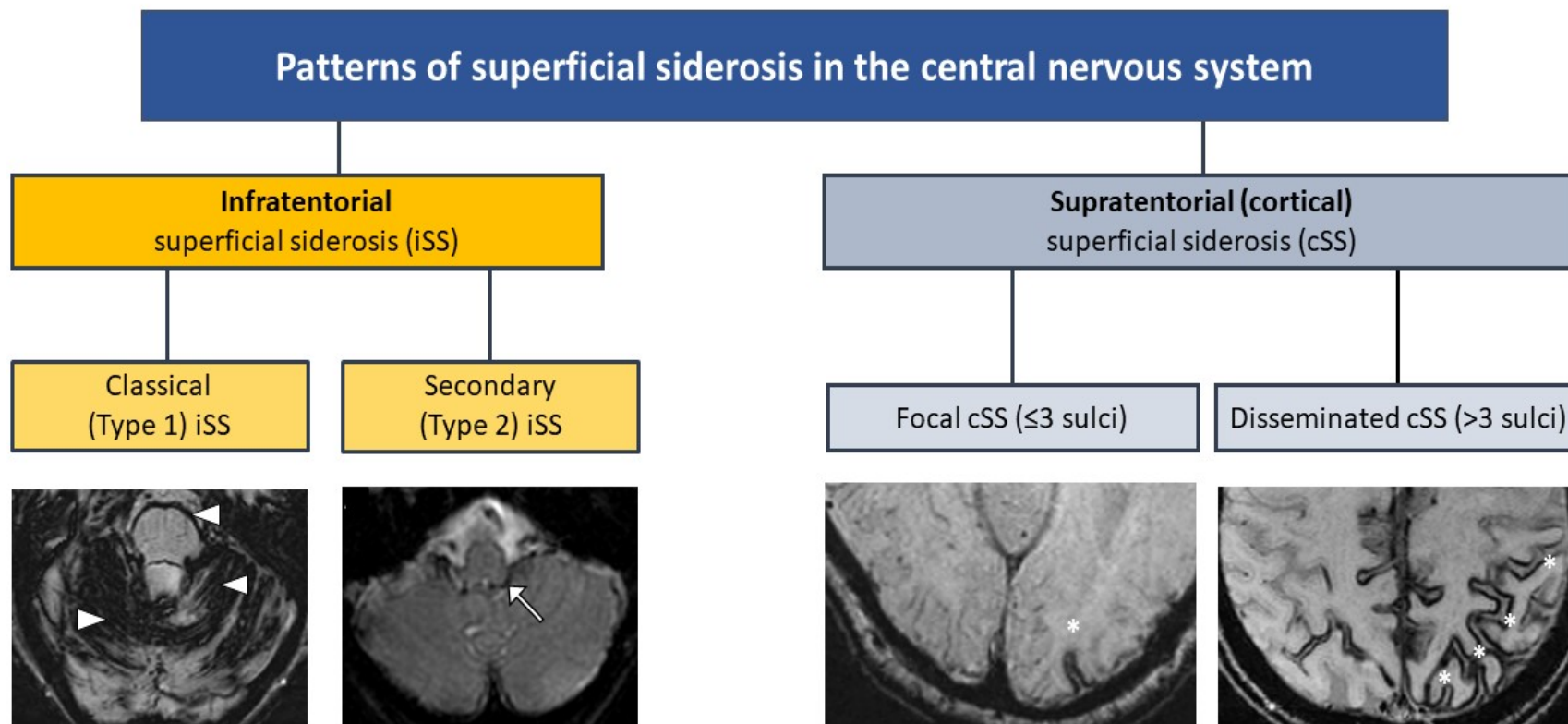
Figure 1.2. Types of superficial siderosis of the CNS (reproduced with permission from Practical Neurology BMJ Journals, under Creative Commons CC-BY 4.0 International license, from Kharytaniuk et al (Practical Neurology, 2022) (14).

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1.4.4 iSS histopathology and pathophysiology

The chronic extravasation of blood into the CSF which characterises iSS is hypothesised to originate from the capillaries or venules at the margins of the dural defect likely following trauma or surgery or at the site of the nerve root avulsions (7, 8, 86). The extravasated blood triggers a cascade of events implicated in the breakdown of red cells. In this process haem is released and it in turn triggers a activation of the iron degradation pathway in which microglia and Bergmann glia are implicated **(Figure 1.3)**. Haem stimulates microglia to release haemoxygenase-1 – a microsomal enzyme that causes the breakdown of haem into biliverdin and free (ferrous) iron (7). Bergmann glia are stimulated to synthesise apoferritin – a protein that binds the free iron and forms ferritin (6, 87, 88). Ferritin is then deposited in the subpial layers in the form of haemosiderin (64, 88). The chronic extravasation of red cells and release of haem overwhelms the iron degradation pathway, resulting in the abundance of unbound toxic ferrous iron which in turn results in lipid peroxidation, gliosis, demyelination and axonal damage (6, 7, 64).

The invariable involvement of the cerebellum including superior vermis, cerebellar flocculus and convexities has been hypothesised to be due to their abundance of central glia and the earliest exposure of the surfaces of these structures to the iron degradation products including free (ferrous) iron in the circulating CSF (8, 89). The preferential involvement of vestibulocochlear (CNVIII) nerves is hypothesised to be due to the exposure of the CNVIII to the CSF, abundance of Bergman glia and microglia, and their long CNS segment and central myelin (8, 64, 90, 91). The transition of CNVIII to peripheral nervous system is marked by porus acusticus which

is the medial opening of the internal auditory canal to where CNVIII travels after

exiting the brainstem at the cerebellopontine angle (64, 91).
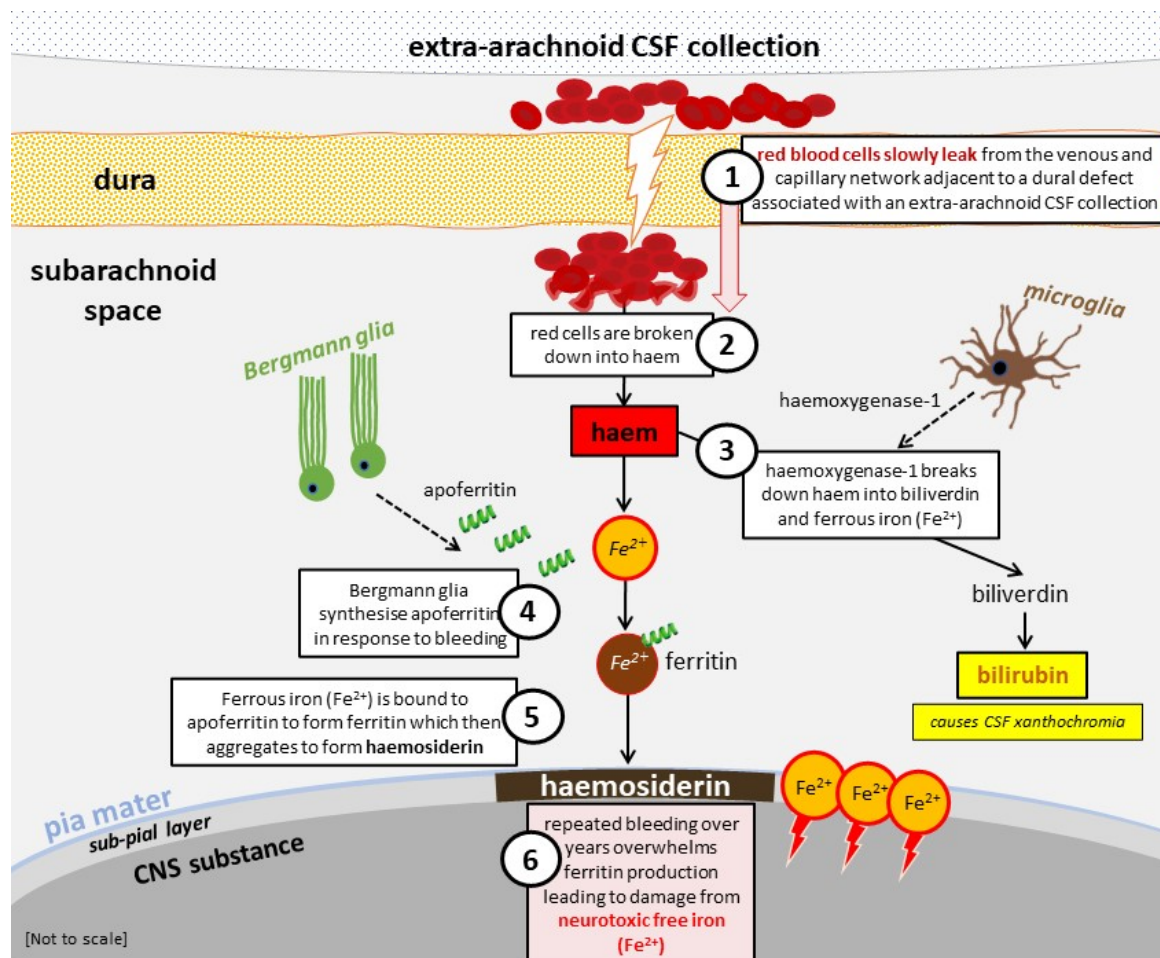
Figure 1.3. Schematic representation of the histopathological processes in iSS. Reproduced with permission from Practical Neurology BMJ Journals, under the Creative Commons CC-BY 4.0 International licence, from Kharytaniuk et al (14).

The involvement of the olfactory (CNI) and optic (CNII) nerves has been reported

albeit infrequently (8). They may undergo similar pathophysiological processes as

those involving CNVIII (64). Olfactory dysfunction has been previously reported in up

to 44% of cases with superficial siderosis (8, 9, 62). In contrast, iSS-related visual

impairment has been rarely described. It has been hypothesised this is due to

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sparing of the macular fibres from the iSS-related pathophysiological processes due to their central location within the optic nerve fibres (14, 66).

1.4.4.1 Temporal bone histological findings

To date, a single case report has been published that describes the temporal bone histological findings from a patient with "superficial siderosis of the CNS". The authors reported the patient had previous history of noise exposure. The report described the atrophy of the strial ganglia, absence of hair cells only in the basal turn of the cochleae bilaterally, and iron deposits involving the stria vascularis, the spiral ligament and the presence of otosclerosis (92). A marked atrophy of the vestibulocochlear nerve was also identified.

1.4.4.2 Animal models of iSS

Several animal studies were able to replicate the deposition of haemosiderin along the surfaces of the CNS structures using iron salts and injections of blood into the CSF (87, 88, 93). Prior to these studies, however, the deposition of haemosiderin was thought to occur as a results of iron overload from a defect in the iron metabolism (8).

1.4.5 Likely causes of iSS

Development of iSS has been associated with a dural defect which may have occurred following CNS trauma or surgery (including surgery for CNS tumours) or at the site of the nerve root avulsions, most commonly from brachial plexus injury; or disorders in which dura may be abnormal such as in certain connective tissue disorders, namely ankylosing spondylitis or Marfan's syndrome (7, 8, 94). More

recently spontaneous intracranial hypotension has been described in the setting of iSS, and the event may precede the onset of iSS. Shievink et al reported a 58% probability of individuals with history of spontaneous CSF leak developing iSS at 192 months follow-up (94-96). Vascular malformations are rarely associated with iSS but have been previously considered to cause iSS (7). A single episode of an acute haemorrhage into the CSF such as subarachnoid, intracerebral or convexity haemorrhages, or following a contusion, or a rupture of a vascular malformation may be associated with other types of superficial siderosis and not the classical iSS clinical features (7, 8).

1.4.5.1 Potential genetic causes of iSS

To date, there have been no familial or genetic links associated with the development of iSS but these have been suggested in the setting of familial cerebral cavernous malformations syndrome (CCM) in which several genes have been implicated (97). CCM is associated with recurrent haemorrhages and radiological features of superficial siderosis in the affected cases (98, 99). Phenotypically, CCM can present with focal seizures, hearing loss has also been described in the affected individuals (100).

Several other genetic conditions in which similar pathophysiological processes for the development of superficial siderosis have been suggested – due to their recurrent subarachnoid haemorrhages. These include Muckle-Wells syndrome (101), Neurofibromatosis Type 1, Marfan's syndrome (102). Hereditary haemorrhagic telangiectasia, Alport, Fetcher, Epstein and Klippen-Trenanay syndromes have also

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been hypothesised to lead to the development of iSS, as small vessels are typically affected in these disorders, there is often associated hearing loss (97, 103-107).

1.4.6 Further investigations

MRI of the entire neuraxis is recommended as part of the diagnostic work-up for iSS (7). It allows to determine the pattern of haemosiderin distribution and thus reach the correct diagnosis, as well as determine the extent of haemosiderin deposits – such as, for example, whether there is supratentorial extension or involvement of the spinal cord. It is also necessary to look for the presence of features suggestive of the aetiology of iSS, such as dural defect, or CSF collection or presence of a pseudomeningocoele (7, 108).

After the radiological diagnosis of iSS is reached the CSF analysis for presence of red cells, elevated levels of ferritin and presence of xanthochromia can confirm active or recent bleeding into the CSF (10, 14, 66, 94).

Further imaging may be indicated for individuals in whom the likely site of dural defect may not be identified on MRI and in such instances the consultation with neuroradiology team may be necessary (7). Such individuals may undergo CT myelogram (CTM) if advised by the neuroradiology team and in whom surgical repair can be considered (7, 108). CTM, dynamic CTM or digital subtraction myelography may be helpful in identifying the source of bleeding particularly if a large spinal CSF collection has been identified on MRI (7, 10). There are however several limitations and risks associated with the use of these imaging modalities including exposure to radiation, contrast extravasation, high costs and limited availability as these modalities may be available in specialist centres.

1.4.7   Management of iSS and associated deficits

1.4.7.1 iSS treatment options

There have been no published guidelines regarding the management of iSS. The clinical care pathway for patients with suspected iSS has recently been proposed by the specialist Superficial Siderosis multidisciplinary clinical team at the National Hospital for Neurology and Neurosurgery, Queen Square, London (14). The group recommended a case-by-case discussion taking into consideration the clinical features and functional status of each patient, and the radiological and CSF findings, as well as any deterioration in the patients' symptoms. The team recommend, following the case discussion, an individualised management plan for each patient which is discussed with the patient (14).

The treatment for iSS is aimed at stopping the bleeding by surgical repair of the dural defect or by removing the likely causative lesion – in cases where the evidence of recent or active bleeding has been confirmed on the CSF analysis, and the decision for surgical repair has been proposed following the discussion the neuro-surgical team. The repair of the culprit lesion and removing of the likely bleeding site is hypothesised to halt disease progression and the associated functional decline (7, 9, 108). Dural blood patching has also been performed and reported in the scientific literature and is a non-surgical option which may be offered by an interventional radiology team. There is limited evidence regarding successful outcomes of this intervention (10, 109, 110).

Another non-surgical option for management of iSS is the use of iron-chelating agents, although these have not been studied in randomised trials. This option may

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be considered for patients who are unwilling or unsuitable for surgery, or those who have had deterioration in their symptoms, or in whom the source of bleeding could not be reliably identified, or for those who have failed surgical repair or the blood patch procedure (9, 14, 108). Both trientine and deferiprone have been used as iron-chelating agents in the setting of iSS. The use of deferiprone, however, has been more widespread compared to trientine which is a copper and an iron chelating agent. In addition to its more targeted chelation, deferiprone has also demonstrated better blood-brain barrier penetration (111). The consideration for use of deferiprone should be carefully weighed against its side effects which include agranulocytosis, neutropenia and sepsis (14, 75, 78, 112-116). To date, there are no randomised trials demonstrating clinical efficacy of these agents, so the evidence is of low quality including subjective patients' reports, MRI appearances of haemosiderin deposits or gait outcomes although currently no validated clinical measures have been identified to monitor treatment response (75, 76, 117).

Involvement of the patient and their family early in the decision-making process is considered best practice in the management of patients with rare diseases (118). It includes discussion about the diagnosis, current knowledge and available evidence to date, the prognosis all while taking into account the patient's preferences and concerns (118). The patient needs to be aware of the current treatment options, and any evidence of their benefits and the associated risks (108, 116, 118).

1.4.7.2 Management of iSS-related deficits

Patients with iSS are likely to have a myriad of symptoms and clinical features. Therefore, it is important to involve specialists from multiple disciplines to provide

appropriate management and address their symptoms, their functional deficits and

needs (14). The input from these clinical disciplines has been advocated by our

specialist Superficial Siderosis multidisciplinary clinical team (14). These include

neurology, neuroradiology, neurosurgery, haematology, neuro-otology and

audiovestibular medicine or ENT teams, cognitive neuropsychology and ataxia

teams, while the involvement of other clinical specialist clinical teams may be

dictated by the patient's symptoms (14).

1.4.7.2.1 Management of hearing deficits

The presence of hearing difficulties is the most common feature of iSS. Individuals

with iSS have reported hearing difficulties in the presence of background noise, as

well as the presence of tinnitus (13, 42). The auditory rehabilitative measures need

to address each patient's specific auditory deficits, taking into consideration the likely

site of the lesion along the auditory pathway. Therefore, a thorough evaluation of the

patient's auditory function is necessary as part of the clinical care (14). The

identification of the affected segment of the auditory pathway will inform appropriate

hearing aiding options which include conventional aids, or cross-routing of signal

(CROS) or bi-CROS hearing aids in the presence of asymmetrical hearing loss. iSS

patients with hearing loss may also benefit from the use of assistive listening devices

such as frequency modulation devices which enhance the person's hearing function

in complex auditory environments and can enhance the function of the hearing aids.

Advice on listening techniques and how to optimise listening environments such as

with reduced reverberation or minimal background noise may be helpful and can be

provided as part of the auditory management plan for the individuals with iSS.

Patients with central auditory processing deficits may also benefit from the use of specialised auditory training. Mindfulness and tinnitus rehabilitative strategies may be necessary for patients in whom tinnitus is intrusive and interferes with their daily activities or sleep.

Cochlear implantation may be considered for the patients who fit the criteria proposed by NICE (119). Cochlear implantation has been described in the setting of iSS, yet to date variable the outcomes have been reported, with successful outcomes described in up to 63% of patients at 12-month follow-up (32, 33, 37, 44, 63, 120-123). The success rates of cochlear implantation may be limited by the progressive nature of the disease and retrocochlear hearing loss. There have been no reports of auditory brainstem implants in iSS patients to date.

1.4.7.2.2 Management of vestibular deficits

Management of iSS-related vestibular deficits, ataxia and imbalance requires input from the neuro-rehabilitative and vestibular physiotherapy teams. Neurophysiotherapy, vestibular and balance rehabilitation are considered the cornerstone in the treatment of imbalance and vestibular deficits and are necessary to maintain and often improve the patient's functional capacity (124-126). A thorough assessment of the vestibular function, identification of patient-specific vestibular deficits and the identification of the likely affected segment of the vestibular pathway, are important for the therapist in order to formulate a patient-specific management plan. Individual exercises need to be put together for each patient to address the patient's imbalance and vestibular deficits. Input from the vestibular physiotherapy

and neurorehabilitation can also be helpful in the management of myelopathy-related spasticity and sensory disturbances.

Patients with poor mobility may benefit from the involvement of occupation therapy. It may help to maintain their mobility levels through the use of special mobility devices and appropriate home arrangements, and for falls prevention.

1.4.7.2.3 Management of other deficits

Cognitive compromise has been demonstrated in patients with iSS, as described above (12). Input from neuropsychological team may provide a baseline measurement of cognitive function and address any cognitive deficits identified. It can be repeated at intervals, as guided by the patient's symptoms (14).

The input from speech and language therapy can be helpful for patients with difficulties with speech production, or those with dysphagia, who in the latter case may also need input from gastroenterology team.

Input from uro-neurology team may be considered in the context of iSS, dictated by the patient's urinary symptoms.

1.4.8   Prognosis and disease monitoring

Although there is currently a paucity of dedicated longitudinal studies, disease progression and functional decline in iSS have been documented. Clinical teams may wish to continue to regularly monitor their patients' clinical status particularly to assess for any evidence of clinical deterioration or onset of new symptoms, and by the respective clinical teams (haematological, neurosurgical) who provide the treatment (14).

Patients may need regular interval audiological evaluation and early rehabilitation of their hearing deficits or adjustments in the current hearing aids according to their most recent hearing thresholds. Similarly, a regular interval follow-up with dedicated neuro- and vestibular physiotherapy teams may require adjustments in their rehabilitative regimes. Input from occupational therapy may also be necessary, in the setting of progressive imbalance and mobility impairment, and to minimise the risk of falls.

There is currently lack of evidence for validated biomarkers or the clinical scales that would allow to objectively assess for disease progression or response to treatment. Although MRI has been used as a modality to monitor interval changes in the appearances of haemosiderin deposits, it has not been validated against the clinical outcomes, and few studies have attempted this in the research setting (75, 76).

1.5   Prevalence

Since the first description in 1908 and until the end of the 20th century, less than 100 cases of superficial siderosis of the CNS had been described. Approximately 300 cases have been described in the last two decades (9). This increase in the recognition of iSS is likely to be explained by the greater accessibility of MRI as well as a recent introduction of paramagnetic sequences which allow even better visualisation of haemosiderin deposits on imaging (7).

Despite the increasing availability of MRI and growing prevalence of iSS, it is considered rare. Its true prevalence is currently unknown (127, 128). Prevalence (i.e., prevalence proportion) is defined as "the proportion of the population with the disease at a specific time-point" (80). This definition is used in the UKB iSS

prevalence study (Chapter 5) as part of this work. Other forms of prevalence (such as "contact prevalence" and "time-period prevalence") were not considered in this work (129-131).

iSS is listed in the OrphaNet Rare Diseases Registry under "Superficial siderosis of the CNS" (ORPHA:247245) (80). In this context it is important to also define the term "rare disease" as variations exist between countries and regions **(Table 1.1)**. The UKB iSS prevalence study (Chapter 5) was performed with the reference to the term "rare disease" adopted by the European Union Commission (1999), which is defined as "affecting fewer than 5 per 10 000 people in a general European population" (132).

Country	Population prevalence	Reference
Australia	50 per 100 000	(133)
China	76 per 100 000	(134)
Europe	50 per 100 000	(132)
Japan	40 per 100 000	(135)
Korea	5 per 100 000	(136)
USA	86 per 100 000	(137, 138)

Table 1.1**.** List of the country- and region-specific definitions of a rare disease (per 100 000 population), adapted under Creative Commons CC-BY 4.0 International licence, from Nguengang-Wakap et al, 2020 (138).

Previous work on the prevalence of superficial siderosis or more specifically iSS, was sought through a literature search, performed using MEDLINE (Ovid) database of MeSH terms: "siderosis" [OR] "hemosiderosis" [AND] "central nervous system"

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[AND] "prevalence". The search was limited to human studies, however without any restrictions to date or language of the publication. The search yielded 30 results. Of those, two studies reported the prevalence of superficial siderosis with infratentorial/cerebellar distribution of hemosiderin.

In a population-based Rotterdam Scan study investigating the prevalence of superficial siderosis in relation to the presence of microbleeds, cerebellar superficial siderosis was identified in 1 of 1062 (0.094%) cases (using 1.5 Tesla field strength, T2*GRE sequence MRI) which was in proximity to the identified cerebellar microbleed (139). In another population-based study from Mayo Clinic Study of Aging (Minnesota), 2 of 1412 (0.14%) residents aged 50-89, were reported to have iSS, identified using 3 Tesla T2-weighted and T2*GRE sequences (86). It was unclear from these studies, if the identified individuals with cerebellar/infratentorial siderosis had the features of the iSS clinical syndrome (86, 139).

An additional literature search identified two further studies. One was an Austrian-based study which aimed to determine the frequency of superficial siderosis in 8843 consecutive MRI brain scans (1.5 Tesla) spanning over a 7-year period (81). Findings of low signal along the surfaces of the cerebral and cerebellar hemispheres, brainstem and spinal cord were identified in 13 cases (in 12, using T2*GRE sequence and in 1 case, using T2-weighted sequence). In 9 cases (of 13), cerebellar haemosiderin was demonstrated involving cerebellum, of whom two (0.02%) had all the clinical features of superficial siderosis: hearing loss and ataxia, and myelopathy (1 case); two (0.02%) additional patients had hearing loss (81).

To date, the largest hospital-based study to report iSS prevalence in 97 733 MRI scans was performed by Friedauer et al. The group identified iSS in 30 (0.031%) cases, and Type 1 iSS was identified in 8 cases (140).

Currently, the prevalence of iSS in the UK is unknown.

1.6 iSS and self-reported health measures

1.6.1 Importance of self-reported measures

Self-report measures allow to determine patient-oriented outcomes, also known as patient-reported outcomes (PRO). They are based on the person's own evaluation of their functional status or their overall health. PRO is defined as "direct subjective assessment by the patient of elements of their health including: symptoms function, well-being, health-related quality of life (HRQoL), perceptions about treatment, satisfaction with care received, and satisfaction with professional communication" (141). Their use is now commonplace in the research and clinical settings. They have been used for various purposes – to evaluate disease-specific health status, determine clinically significant changes, monitor disease progression and assess for treatment response or assess the patient's quality of life, some can be used alongside such health-related measures as morbidity, survival outcomes and disease-specific biomarkers (142-144).

World Health Organisation (WHO) defines quality of life as "the individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (145). In the scientific literature, however the terms "quality of life", "health-related

quality of life" and "health status" have been used interchangeably (146). Several definitions exist that define "health-related quality of life" (143, 147-149), however none seem to clearly distinguish between quality of life and health (146). The National Institute for Health and Care Excellence (NICE) defines health-related quality of life (HRQoL) as "a combination of a person's overall physical, mental and social wellbeing, not merely the absence of disease" (150).

Assessing health-related quality of life (HRQoL) is well-recognised as an important PROM as it allows to report "the status of a patient's health condition that come directly from the patient without interpretation of the patient's response by a clinician or anyone else" (143, 151). Such measures reflect the overall functional status and the impact of a disease on an individual (152, 153). They can be generic or disease- or condition-specific (143, 144). The generic measures offer versatility in their application and can be used for populations with different disorders. The condition-specific HRQoL measures may be more accurate in reflecting the patients' functional status by including within the measure the domains that are condition- or disease-specific and therefore may be more likely to better reflect HRQoL or may even be able to record significant clinical changes associated with monitoring treatment response or disease progression (153-155). A variety of HRQoL PROMs has been used in certain rare genetic disorders (156, 157). The correct choice of instruments to measure HRQoL is important, as they must be suited to the studied population, and line up with the aims of the research study or clinical activities.

Currently, EuroQol 5-Dimensions (EQ5D) is recommended as a HRQoL tool by the UK National Institute for Health Care and Excellence (NICE). Its domains reflect the

definition of HRQoL proposed by NICE. (146, 149). EQ5D was first developed in 1990 (158). It has been demonstrated to have good psychometric properties and low respondent burden and is considered a good generic tool to assess HRQoL (159-161). It has been used in a variety of settings and in different populations with chronic conditions, as well as for benchmarking of services in the in the UK's National Health Service (NHS) (156, 158-162). The original version of EQ5D contained 3-level severity scoring and was reported to have limitations, with the ceiling effect being one of them (163). This was overcome by further development of the instrument which now includes a 5-level (5L) severity scoring. The latter has been demonstrated to have a good construct validity and adequate reliability and can be applied to different populations (156).

The limitation of generic HRQoL instruments, is that they include a set of attributes (domains) that might not overlap with those that are typically affected in a specific disease. In contrast, dedicated instruments, focus on the specific domains. Their use is recommended for targeted populations, including the recommendation by NICE (153-155, 164). To date, no dedicated iSS HRQoL PROMs exist. In the absence of dedicated condition-specific HRQoL instruments, NICE recommend the use of generic HRQoL measures which include the domains likely to be impacted by the disease to better capture the full impact of the disease on HRQoL (164).

Health Utilities Index-Mark III (HUI3) is a generic HRQoL measure which, in addition to the domains that are included in EQ5D, like mobility and pain, also includes such domains as hearing, cognition, vision, speech, dexterity and emotion. These domains are not included in EQ5D but may be affected in individuals with iSS. It is

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thus possible that HUI3 may be a better instrument to capture HRQoL in iSS than EQ5D. HUI3 has been suggested as a more suitable HRQoL measure than EQ5D in hearing-impaired individuals (165). EQ5D has been demonstrated to be less sensitive to changes in HRQoL in individuals with severe to profound hearing loss, which can also be a feature in individuals with iSS (165, 166). Furthermore, HUI3 has also been demonstrated to be more responsive to changes from interventions for hearing loss, such as hearing aids and cochlear implants (165, 167, 168). Neither HUI3 nor EQ5D however has shown superiority of one over the other instrument, and it has been recommended that both EQ5D and HUI3 are used in assessing benefits from hearing-rehabilitative interventions (169). Both these instruments assess different aspects of HRQoL: EQ5D determines the HRQoL with regards to the individual's performance status whereas HUI3 allows to determine the utility scores based on the level of the individual's functional impairment.

Because hearing loss is one of the most commonly reported symptom in iSS, it may be useful to include the PROMs that are hearing-specific, alongside the generic HRQoL instruments (8). A variety of dedicated hearing-specific measures are available to date and their use is often dictated by the purpose of the assessment and the parameters which need to be measured (165, 170, 171). Several hearing-specific PROMs such as modified Amsterdam Inventory for Auditory Disability and Handicap (mAIADH) and Speech, Spatial and Qualities of hearing scale (SSQ) have been used in clinical populations with auditory processing deficits and thus might help to assess for presence of auditory processing deficits in individuals with iSS (170, 172, 173). This is important because central auditory processing deficits have

been demonstrated in a patient with iSS, and they may be a feature of iSS-related

auditory dysfunction however this has not been studied to date (43).

ERSA (full title "Evaluation du Retentissement de la Surdité chez l'Adulte: evaluation

of the impact of hearing loss in adults") was recently developed as a self-reported

tool that allows evaluation of the impact of hearing impairment and the use of

rehabilitative interventions on HRQoL (171). It has been validated for use in hearing-

impaired working and retired populations, with or without hearing aids or cochlear

implants (13, 42). ERSA is a self-report instrument that can be used by individuals

with hearing problems of various degree. Because of the heterogeneity in hearing

levels of in individuals with iSS, ERSA may be a suitable hearing-specific PROM.

ERSA was chosen over other dedicated hearing-specific questionnaires such as the

Glasgow Benefit Inventory (GBI) or the Abbreviated Profile of Hearing Aid Benefit

(APHAB) which have been developed specifically for populations who have

undergone ear surgery or have received hearing aiding, respectively. These two

instruments have also been shown to have response rates lower than ERSA (171).

Tinnitus Functional Index (TFI) is a self-report measure that assesses the impact of

tinnitus on the individual's QoL and daily functioning (174). Tinnitus which is

described as "perception of sound in the absence of external stimulus" is a common

phenomenon associated with hearing loss and is often reported in older populations

and has also been reported in individuals with iSS (175-177). Tinnitus may impact

the ability to hear and may also have a negative effect on HRQoL (178, 179).

Although over 100 tinnitus questionnaires have been developed to date, the majority

of those focus on assessing tinnitus severity (180, 181). TFI has been suggested as

a useful outcome measure in populations with tinnitus in clinical and research settings (174, 181).

1.6.2 Challenges related to the use of self-reported measures

Due to the multifactorial and progressive nature of iSS, it may be difficult to accurately determine the patient-reported outcomes, as significant variations may exist between the individuals with iSS which is possibly due to their differences in symptom burden and functional status, and perhaps reflecting the different rates of disease progression, as well as due to the presence of co-morbidities. Nonetheless, assessment of HRQoL can provide information on the overall health status in iSS. The scores may be used as a reference point at the time of diagnosis, or considered as a monitoring tool for disease progression or response to treatment and to the rehabilitative measures (182). The use of hearing-specific measures may be helpful in identifying iSS-specific hearing profile.

There have been no studies to date to determine the HRQoL in individuals with iSS. There is, therefore, a need to determine the overall health status and the degree of functional impairment in iSS, and specifically with regards to hearing. Equally, because iSS-related hearing loss may be likened to ARHL, there is a need to identify markers that would differentiate between iSS-related hearing loss and ARHL and the self-reported measures obtained for individuals with iSS and ARHL may be such tools to use, in addition to the objective clinical markers of iSS.

1.7 iSS in the spectrum of other complex neuro-otological disorders

Due to its rarity, iSS may be under-reported and clinicians may be less aware of this entity than of other rare neuro-otological disorders. It is likely that the prevalence of iSS will continue to increase due to more widespread availability of MRI, and thus there is a need to increase clinicians' awareness of iSS. It should be considered as a differential diagnosis when evaluating complex neurological patients with audiovestibular deficits. These patients should undergo dedicated neuro-otological work-up, similarly to patients with other rare neurodegenerative disorders of hearing and balance. They often need multidisciplinary input in the management and rehabilitative support of their audiovestibular deficits. Such similar conditions include Friedreich's ataxia (FRDA), Charcot-Marie-Tooth disease (CMT), spino-cerebellar ataxia (SCA), and cerebellar ataxia, neuropathy and areflexia syndrome (CANVAS) (128, 183). It is, therefore, important that iSS is recognised in the clinical setting to be on the par with these and other rare complex neuro-otological conditions.

1.8 Knowledge gaps and rationale for this project

Despite iSS being considered rare, our clinical knowledge and research-based evidence regarding iSS have been growing in the past several decades, yet research opportunities remain limited and gaps in the knowledge exist.

In addition to the lack of dedicated studies on natural history of iSS, there is a dearth of evidence regarding the use of objective clinical measures and biomarkers to aid the diagnosis of iSS, measure disease burden or monitor its progression or response to treatment over time.

1. The most common features of iSS are considered to be hearing loss, ataxia and imbalance. Phenotyping of audiovestibular function in iSS is necessary to establish iSS-specific audiovestibular features, identify the likely involved segment along the audiovestibular pathway which can help to understand the pathophysiological processes in iSS. From a clinical perspective, identifying salient audiovestibular features in iSS would allow iSS to be recognised on the same par as other complex neurodegenerative conditions in which hearing and balance are affected, as such patients need to be seen in dedicated neuro-otological clinics due to their likely complex audiovestibular deficits and needs. A better understanding of the pathophysiological processes and a more comprehensive knowledge of the audiovestibular deficits are both necessary for clinicians when formulating auditory and vestibular rehabilitative strategies for patients with iSS-related audiovestibular deficits. Assessment of the auditory and vestibular functions may also provide a useful baseline measure against which the deterioration in the audiovestibular function may be measured over time.

2. Assessment of the olfactory function may help better understand the involvement of CNI in iSS. Olfactory dysfunction may also be a feature of iSS. It is likely that the CNI is subject to the same pathophysiological processes as those involving CNVIII and the olfactory dysfunction may correlate with hearing loss. The prevalence of olfactory dysfunction in iSS population has not been studied to date.

3. Currently, the choice of markers that can contribute to the diagnosis or assess symptom load in individuals with iSS or as a means to monitor disease progression and response to treatment, is limited to MRI findings and subjective patient reports.

There is limited evidence demonstrating response to treatment as a reduction in haemosiderin burden observed using MRI. Few attempts have been made to quantify haemosiderin on MRI, with these techniques used in the research settings. However, a measure that can quantify haemosiderin deposits as visualised on MRI which can be easily implemented in the clinical and research settings is still lacking.

4. It also remains to be established whether measuring the haemosiderin burden as visualised on MRI can be used as a proxy for disease burden and functional impairment. Markers that can objectively assess the functional status in iSS and which are more widely and easily available and are sensitive to detect subtle clinical changes have not yet been identified. Correlation of the audiovestibular function in iSS with the imaging findings has not been formally studied to date.

5. PROMs should be considered for inclusion into the research studies and clinical evaluation of patients with iSS – as adjunct measures to capture the patients' functional status and likely disease burden. Such PROMs may include HRQoL instruments. HRQoL has not been studied in individuals with iSS. Use of generic HRQoL measures is necessary as iSS-specific PROMs are currently lacking.

Additionally, the use of dedicated hearing-specific PROMs may help to understand the impact of hearing dysfunction in individuals with iSS. It may also help identify iSS-specific auditory deficits as an adjunct measure to the auditory testing which can be undertaken by the conventional auditory test battery commonly available in the clinical setting.

6. With increasing MRI availability, iSS has become more frequently recognised and thus diagnosed. Yet limited evidence exists regarding its prevalence in the general population, and no studies to date have estimated iSS prevalence in the UK.

1.9 Hypotheses

This work was based on the hypotheses that:

1. iSS-specific auditory and vestibular characteristics may exist, reflecting the involvement of specific segment of the audiovestibular pathway, and the iSS auditory (including from hearing-specific PROMs) and vestibular phenotypes may help distinguish iSS from other neuro-otological conditions or ARHL.

2. It may be possible to identify the most likely affected segment of the audiovestibular pathway – through a comprehensive assessment of the audiovestibular function in individuals with iSS.

3. The involvement of CNI and CNVIII may be synchronous, and the olfactory dysfunction may be more common than anticipated and correlate with the auditory function in individuals with iSS.

4. The audiovestibular function – represented by the hearing thresholds and the presence or absence of vestibular deficits – may correlate with the appearance of haemosiderin on MR imaging and may also reflect the involvement of central auditory and vestibular cortical structures.

5. Cerebellum and in particular superior cerebellar vermis may be the most frequently affected region of the CNS by the haemosiderin deposits, which can be assessed using brain MR imaging.

6. iSS may negatively impact the HRQoL of the individuals with iSS and those with ARHL.

7. The prevalence of iSS may be similar to the prevalence of other complex neurodegenerative conditions in which audiovestibular impairment is common.

1.10 Aims of this work

To address the hypotheses outlined above, the following aims were set out as part of this work.

1. To comprehensively describe the audiovestibular function of iSS (Hypothesis 1), by collating the results of the commonly used audiological and vestibular clinical tests and comparing the auditory and vestibular test findings with the normative data (Appendix 1). This aim underpins the AViSS study, described in Chapter 3 of this work.

2. To determine the prevalence of olfactory dysfunction in individuals with iSS and whether the degree of the olfactory dysfunction correlates with the hearing thresholds (Hypothesis 3). This aim underpins the AViSS study described in Chapter 3 and can be achieved by assessing the olfactory function in a group of patients with the radiologically and clinically confirmed iSS using a validated smell test and by determining if association exists between the results of the olfactory test and the hearing thresholds.

3. To locate the likely affected segment of the auditory and vestibular pathways based on the results of the clinical tests and based on the imaging findings (Hypotheses 2 and 4). This aim underpins the AViSS and QUASARS studies described in Chapters 3 and 4, respectively. The aim can be achieved by comparing the audiovestibular function in individuals with iSS with the corresponding MR images of these individuals.

4. To identify the imaging biomarkers and determine if correlation exists between the imaging markers and the markers of audiovestibular function (Hypotheses 4, 5 and 6). This aim underpins the AViSS and QUASARS studies described in Chapters 3 and 4, respectively. This aim can be achieved by creating an imaging rating tool (scale) that could quantify the intracranial appearance of haemosiderin deposits, systematically describing the radiological distribution of haemosiderin deposits, and assessing for presence of correlation between the imaging rating scale scores and the audiovestibular function.

5. To identify the auditory markers, including through hearing-specific self-reported measures (PROMs) which would distinguish iSS-related hearing loss from ARHL (Hypotheses 1 and 2). This aim underpins the AViSS and QoL in iSS and ARHL studies described in Chapters 3 and 6, respectively. This aim can be achieved by comparing the scores of the hearing-specific self-report measures between the group with iSS and the group with ARHL.

6. To determine the impact of iSS on HRQoL and with regards to hearing dysfunction (Hypothesis 6). This aim underpins the QoL in iSS and ARHL study which is

described in Chapter 6. This aim can be achieved by calculating the scores that

represent the overall health status from two common generic HRQoL measures.

7. To determine the prevalence on iSS in a large sample of general UK population

and compare it to the published prevalence of other neuro-otological conditions

(Hypothesis 7). This underpins the UKB iSS prevalence study which is described in

Chapter 5. It can be achieved by reviewing the brain imaging of participants from the

UK Biobank study, representing a large general UK population sample, and

calculating the number of cases which are identified with the radiological features

suggestive of iSS.

1.11 Thesis structure

This work includes four research studies which follow Introduction (Chapter 1) and

Methodology (Chapter 2) sections.

Chapter 3 (AViSS study) focuses on the audiovestibular characteristics in iSS. This

was achieved by combining the findings from the clinical data from a large cohort of

individuals with radiologically confirmed diagnosis of iSS and who were under the

care of the specialist Superficial Siderosis multidisciplinary clinical team from the

University College London Hospitals (UCLH) National Health Service (NHS)

Foundation Trust and from the dedicated research study to ascertain the

audiovestibular function in individuals with iSS.

Chapter 4 (QUASARS study) describes the development of a new imaging rating

scale proposed as an objective measure to radiologically quantify the intracranial

haemosiderin appearances. The study assesses the instrument's reliability and

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explores its applicability by attempting to evaluate the imaging findings in the context of the patients' audiovestibular function.

Chapter 5 (UKB iSS prevalence study) investigates the prevalence of iSS based on the imaging findings suggestive of the radiological features consistent with the diagnosis of iSS from a large general population sample obtained from the UK Biobank study (a large health-related and imaging data repository).

Chapter 6 (QoL in iSS and ARHL study) explores the impact of iSS on the overall HRQoL and hearing function in individuals with iSS by means of PROMs, in order to describe disease burden and hearing function in iSS, and it compares the results from the iSS group with those from individuals with ARHL (as a control group) and attempts to identify distinguishing auditory features between iSS and ARHL.

Chapter 7 (Discussion) follow the research chapters and includes the overall findings in the context of currently available evidence. It also discusses the limitations of this work and proposed directions for future research.

CHAPTER 2   METHODOLOGY

MATERIALS AND METHODS

2.1   Study design and settings

The research projects included in this work were carried out in a variety of settings.

2.1.1   AViSS and QUASARS Studies (Chapters 3 and 4)

The AViSS and QUASARS studies are descriptive cohort studies and include the clinical and imaging data from the clinical database of patients diagnosed with iSS who have been under the care of or reviewed by the specialist Superficial Siderosis multidisciplinary clinical team (MDT) at the Queen Square National Hospital for Neurology and Neurosurgery, Queen Square (UCLH NHS Foundation Trust), London. The team included senior clinicians: Professors DJ Werring, RH Jäger and DE Bamiou, Drs P Cowley, SF Farmer, P Eleftheriou, E Chan, Mr P Sayal and several others.

The original database has been compiled by the team and was used to ascertain the radiological features of patients with iSS (7). The findings were summarised and formed the basis for the proposal of the iSS radiological diagnostic criteria (7). Initially, patients were identified through the search of the term "superficial siderosis" within the neuroradiological reports of neuroimaging which had been undertaken at the National Hospital for Neurology and Neurosurgery, Queen Square, London between the 30th of June 2004 and the 30th of January 2014. The database was then prospectively populated by the Superficial Siderosis multidisciplinary clinical team to include patients referred to the clinical team with suspected iSS from the 20th

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September 2013 (7)**.** The database was expanded as additional patients were added prospectively by the Superficial Siderosis clinical team, until the 31st of December 2021.

In addition to the clinical patient cohort, a research study was rolled out titled AudioVestibular function in infratentorial Superficial Siderosis (AViSS). AViSS was initially planned as the main research project. Due to the low recruitment numbers in this research study and the limitations with the time frame which were impacted by the COVID-19 pandemic, the findings from both the clinical data collected by the clinical team and the data obtained as part of the research study were combined to achieve a comparatively large sample size. The findings are presented in Chapter 3 as the AViSS study. The analysis of the clinical data was performed as part of the clinical audit activity. The research study protocol was developed following the STROBE guidelines for reporting of observational studies (184).

The participants of the research study – who were also the patients under the care of the Superficial Siderosis multidisciplinary team and had been invited to participate in and recruited to the study – underwent the audiovestibular testing in the clinical area of the Department of Neuro-otology and Audiovestibular Medicine at the Royal National ENT and Eastman Dental Hospitals (UCLH NHS Foundation Trust), London.

The clinical imaging was performed as part of the clinical care pathway for the patients diagnosed with iSS and under the care of the Superficial Siderosis multidisciplinary team at the National Hospital for Neurology and Neurosurgery (UCLH NHS Foundation Trust). The imaging took place either at the Trust or

externally (elsewhere, usually the patients' local imaging facility) and in which cases it was migrated to the Trust's clinical picture archiving and communications system (PACS) using secure clinical imaging exchange portal (IEP, Sectra, UK). MR images of head/brain and, where available, of internal acoustic meati (IAMs) and performed between September 2006 and the 31st of December 2022 were accessed as part of this project. Both T2-weighted and paramagnetic-sensitive sequences were available in the majority of cases. Earlier images had been archived and could not be retrieved for this project.

2.1.2   UKB iSS Prevalence Study

This is a cross-sectional study in which the data were obtained from the UK Biobank (UKB) database. UKB database had been created as part of a large-scale prospective cross-sectional study of health and disease determinants in a large non-hospital UK population sample (185). In addition to the population characteristics such as socio-demographic data, lifestyle factors, past medical history and self-declared health-status, imaging data were also collected. (186). The UKB imaging data included MR brain imaging; paramagnetic-sensitive (SWI) sequence images were available and were reviewed by the researcher as part of the UKB iSS prevalence study (Chapter 5).

2.1.3   QoL in iSS and ARHL Study

This is a single-site cross-sectional case-control study set up as an anonymous online survey using the Research Electronic Data Capture platform (REDCap, Vanderbilt, the Netherlands) licensed to UCL. The study protocol was developed following the STROBE guidelines for reporting of observational studies (184).

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It was decided to use an online survey system as it would allow participation of individuals in remote geographic locations and thus overcome the challenges associated with reaching out to such populations and lower costs of study delivery (187, 188) and in view of social distancing and public activity restrictions in place due to COVID-19. This approach may have also reduced bias associated with face-to-face completion of questionnaires and increased completion rates (189). The survey contained study-specific questions on demographics and hearing which were followed by the generic PROMs on the overall HRQoL and hearing-specific PROMs. In anticipation of survey fatigue, the questionnaires were presented in set order, with the shortest and most frequently used presented early in the survey.

2.2 Study population eligibility criteria, recruitment, and consents

2.2.1 AViSS Study

The AViSS research study recruitment took place between November 2020 and July 2021. The patients were advised by the clinical team of the research study taking place. Patients interested in the study were contacted by the clinical research fellow and provided with the study information. They were given the opportunity to familiarise themselves with the study information for at least 24 hours and were offered the opportunity to ask questions about the study. Due to COVID-19 pandemic, all the documents for the study were distributed electronically and by post with pre-paid self-addressed envelopes. Formal written consent to participate in the AViSS study was obtained from each participant as part of the study enrolment and prior to study-related activities. All participants were reviewed by the clinical researcher during their visits to the testing facilities. Verbal consent from all the

individuals was obtained prior to undertaking the audiovestibular testing, which is the standard practice within the department.

2.2.2 QUASARS Study

The data collected for the QUASARS study was from the clinical imaging from the same clinical database of the patients diagnosed with iSS, as for the AViSS study.

MR imaging of the brain/head was reviewed which followed this (inclusion) criteria: MR imaging was:

- Of patients who had been diagnosed with iSS and under the care of the Superficial Siderosis multidisciplinary team (as specified earlier) and who underwent auditory or vestibular testing or both;
- T2-weighted or paramagnetic-sensitive (T2*GRE or SWI) sequences or both;
- Performed within the shortest time interval from the audiological or vestibular tests;
- Free of any significant imaging artefacts and would allow the visualisation of all anatomical regions included in the QUASARS scale.

The MR imaging was not reviewed as part of this study in the following cases (exclusion criteria). MR imaging was:

- Other than the brain/head; for example, spinal MRI;
- Of the patients diagnosed with other types of superficial siderosis rather than classical iSS, for example cSS;

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- With an artefact that would not allow visualisation of all the anatomical regions included in QUASARS score, for example MRI IAMs where MRI brain/head is not available or MRI with an artefact for example from a cochlear implant;

- Of the patients who did not undergo either auditory or vestibular assessments or whose test results were not available or not retrievable.

2.2.3 UKB iSS Prevalence Study

This study included imaging data accessed following a formal application to the UK Biobank (UKB). The data were collected and stored by the UKB group. Over 500 000 participants aged 40-69 were recruited for the UKB study; consents from participants were obtained by the UKB team (186, 187). Recruitment was performed by the UKB team across the UK through the National Health Service and is described in detail elsewhere (185). The imaging for the UKB study was acquired by the UKB team and performed for up to 50 000 UKB study participants. The UKB team created image-derived phenotypes using automated image processing pipelines to remove artefacts and ensure compatibility of images between the UKB imaging study participants (190).

2.2.4 QoL in iSS and ARHL Study

The study recruitment commenced after receiving the institution's Research Ethics Committee approval. The study was then set up on the REDCap platform. It was open for recruitment between the 20th April 2020 and the 31st July 2021. Dedicated iSS and ARHL patient groups, charities and organisations were contacted to share the information about the survey and invite individuals with iSS and with ARHL to participate. The recruitment was simultaneous for both groups.

2.2.4.1 Superficial siderosis group (iSS group)

Dedicated patient groups, charities and organisations within and outside the UK, were contacted to share the information about the study and invite their members with the diagnosis of iSS to take part in the study.

2.2.4.2 Group with age-related hearing loss (ARHL group)

Relevant age-related national charities were contacted, including the University of Third Age (U3A, London and Ealing) to disseminate information about the study.

The relevant charities, organisations and patient groups who agreed to disseminate information about the study were provided with the study recruitment information pack: (1) a poster bearing the study title, study-specific information, an online link for the study, QR and study's access code, and the researchers' contact details; and (2) participant information sheet (which was also available online).

Individuals interested in the study were invited to follow the link to the study pages. The first page contained the same participant information sheet provided with the recruitment pack, as well as the online consent form. Prior to commencing the survey, potential participants were invited to read the information sheet. Individuals interested and willing to participate in the study were then asked to confirm that they had read the information provided, that they were of 18 years or older and that they consented to take part in the study. The consent form was provided in an electronic format so that every box needed to be ticked by the potential participant before the consent form was considered complete. By ticking all the boxes in the consent form, only then the participant would have been able to proceed to the study webpages.

Individuals who did not confirm they read the information sheet nor their eligibility for the study, nor provided full consent to participate in the study, could not proceed to the survey webpages and thus could not take part.

The study eligibility criteria were:

1. Confirmation that the potential participant read the participant information sheet;

2. Age: ≥ 18 years;

3. Diagnosis confirmed by a health-care professional:

   - For iSS group: diagnosis of infratentorial superficial siderosis (also known as superficial siderosis of the central nervous system);

   - For ARHL group: diagnosis of ARHL;

4. Consent to participating in the study.

It was deemed not necessary to specify the age bracket for recruitment of ARHL participants. While the prevalence of hearing loss is known to be the greatest in older populations (191), the onset of hearing problems can occur earlier, with the increase in incidence and prevalence of hearing loss (in the 40 year-olds and older groups) demonstrated in double figures (192-194). However. Coupled with the ageing processes, ARHL is known to occur due to a variety of auditory stresses, including noise exposure and other lifestyle and environmental factors, or due to presence of co-morbidities, genetic predisposition, and coupled with ageing processes (192, 195). Different cut-off levels for older age, commonly referred to the person's chronological age, exist but is usually referred to as 65 years or older. The United Nations, however, refers to older age population as: of 60 years old or older, with the similar cut-off age adopted by Davis et al (191, 196, 197). Therefore, the participants

from ARHL were not excluded based on their age but if they confirmed that their hearing loss was deemed by a health-care professional due to age-related changes, even if diagnosed before the age of 60 years.

2.3 Data collection and storage

2.3.1 AViSS Study and QUASARS Study

The clinical data were obtained from the clinical records of the patients who had been under the care of the Superficial Siderosis multidisciplinary team from June 2004 to December 2021). The clinical imaging was reviewed using PACS system accessed either on-site or remotely using the Trust's secure encrypted system.

Anonymised datasets were generated as part of this work and were used for statistical analysis. Personal identifiable information was stored in the Data Safe Haven which is a secure encrypted online platform provided by UCL for the duration of the project.

Data collection included:

- Patients' characteristics (age at the time of the test or scan; disease duration – defined as time interval calculated (in years) from the likely event to have caused iSS, to the year when the test or the scan were performed);

- Results of auditory assessments for right, left and both ears: PTA averages for 3-frequency (3FA: 0.5/1/2 kHz) and 4-frequency (4FA: 0.5/1/2/4 kHz). To calculate 3FA and 4FA where thresholds were not reached at 120 decibel Normalised Hearing Level (dB NHL), the values were substituted with 120 dB NHL value, which is described in detail in Section 2.5.1.

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- Results of vestibular assessments which are described in detail in Section 2.5.1;

- QUASARS scores from the 30 scans (for T2-weighted and paramagnetic-sensitive sequences each) which were reviewed by both raters (to calculate the inter-rater agreement); and the scores from the 10 scans (for T2-weighted and paramagnetic-sensitive sequences each) which were reviewed by both raters (to calculate the intra-rater agreement);

- QUASARS scores from the scans of the study's cohort (to calculate pooled scores, including mean/median scores, and frequency of involvement of certain anatomical regions) which were reviewed by the researcher (NK).

2.3.2 UKB iSS Prevalence Study

The UKB data had been anonymised at source. The images were de-faced by UKB team to protect participants' identity (198). Where the participants subsequently withdrew from the UKB study, the researcher was notified by email from the UKB group and the respective data were excluded from the analysis, in line with the UKB protocol (190).

Upon obtaining the permission to access the UKB database, data were downloaded from the UKB server to the UCL Remote Data Storage (RDS) facility.

2.3.3 QoL in iSS and ARHL Study

Data were collected and outputted using REDCap software licenced to UCL. The data were anonymous at the outset. Codebooks for data collection were created for each instrument.

Outputted data were reviewed for duplicate and incomplete entries which were excluded from the analysis. Ambiguous or inconsistent entries pertaining to the participant's diagnosis, such as inconsistency between the diagnosis indicated in the consent form and in the study specific question were also excluded from the analysis (two cases). Entries from participants in the ARHL group who indicated the onset of hearing problems at an early age (<40 years old) and had additional risk factors for hearing loss which included family history of early onset hearing loss, previous ear surgery, and history of otorrhea were also excluded (two cases).

2.4 Materials

2.4.1 Equipment for AViSS Study

2.4.1.1 Audiovestibular testing

Regular calibration of the auditory and vestibular departmental equipment was performed, including prior to all the testing where necessary, in line with the recommendations from the British Society of Audiology (BSA) or the equipment manufacturers and in keeping with the departmental standard operating procedures.

The following equipment was used to test the audiovestibular function of the patients' and the research study participants' (from June 2004 to December 2021).

2.4.1.2 Auditory testing

Pure-tone audiometry was performed using one of the following audiometers:

GSI (Audiostar Pro, 61; Otometrics (Auricle, Astera); Interacoustics: KC50, AC40, and using TDH-39 headphones.

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Tympanometry/middle ear analyser and acoustic reflex testing was performed using one of the following systems: Madsen Zodiac (Otometrics); GSI (TympStar V1, V2; 38 V2).

Otoacoustic emissions were assessed using ILO V6 dual channel (Otodynamics).

Auditory brainstem reflex testing was performed using one of the following evoked potential systems: Caldwell Sierra (Wave; Summit); Synergy (Viasys); Neurosoft (Otometrics); Nav Pro. The stimuli were presented via TDH-39 headphones (transducers).

Speech audiometry (speech-in-quiet) testing was performed by presenting pre-recorded Arthur Boothroyd (AB) wordlist using a CD player via GSI 61 audiometer and TDH-39 headphones.

Central auditory tests were assessed by presenting pre-recorded lists using CD players: CD 5 V3.0 (Cambridge Audio); Sony CD Player; Gemini Comp-1400; GSI 61 audiometer; Phonak pre-installed software (LiSN-S). The stimuli were presented via Sennheiser or TDH-39 headphones.

2.4.1.3 Vestibular testing

Video Head Impulse Test (vHIT) was assessed using ICS Impulse (Otometrics).

Bithermal caloric irrigation test was performed using one of the following systems: Difra, Synapsys, Micromedical Visual Eyes 525 System (OtoAccess), NyStar ENG System. These same systems were used for oculomotor and rotation chair testing for

videonystagmography (VNG) or electronystagmography (ENG, using NyStar ENG System or Difra ENG system). System 2000 or Orion rotatory chairs were used.

Vestibular Evoked Myogenic Potentials (VEMP, ocular, cervical) were tested using one of the following evoked potential systems: Caldwell Sierra (Wave; Summit); Synergy (Viasys); Neurosoft (Otometrics); Nav Pro. The stimuli were presented using TDH-39 transducers for air conducted testing. Electrode pre-amplifier, Bruel and Kjaer mini shaker 4810 and 2718 power amplifier were used for bone-conducted testing.

2.4.1.4 Olfactory testing

The smell test was performed using the University of Pennsylvania Smell Identification Test (UPSIT, 40-item, British version), acquired from Sensonics™ INC (199). Each kit was in a sealed envelope containing four booklets and a pencil; all kits were checked for expiration date and were within the use by date.

2.4.2 Equipment for QUASARS Study

Due to the remote nature of the study, the PACS medical imaging viewer was used for remote access. The imaged were viewed in semi-dark conditions by the researcher using the LG UltraFine 4K 23.7-inch display monitor (2019, LG UK). To assess the inter-rater reliability, the images were viewed in semi-dark conditions by the two raters using dedicated PACS workstations at the Trust's imaging viewing suites. The images were viewed on the AGFA IMPAX PACS System 3-megapixel diagnostic display Barco Coronis 3MP monitors.

The T2-weighted and paramagnetic-sensitive MR sequences were reviewed to collect the imaging data. The MR images were acquired at multiple imaging suites at the Trust with MRI machines from several vendors; external imaging was performed by other units and in such cases was migrated onto the Trust's PACS system using a secure clinical imaging exchange portal (Sectra IEP, UK).

2.4.3   Equipment for UKB iSS Prevalence Study

Susceptibility-weighted (SW) MRI scans were acquired at three different sites using identical 3 Tesla Siemens Skyra MRI scanners (software platform VD13) with 32-channel head receive coils. SW MRI data were acquired using a three-dimensional (3D) dual-echo gradient echo sequence with the following parameters: voxel size=0.8×0.8×3mm3, matrix size=256×288×48 (whole-brain coverage), echo times (TE1/TE2)=9.4/20ms, repetition time (TR)=27ms, in-plane acceleration=2 and total scan time=2 min 34 s (186, 200). The imaging protocols are described in **Table 2.1.**

UKB SW MR mages were available in DICOM (Digital Imaging and Communications in Medicine) and NIFTI (Neuroimaging Informatics Technology Initiative) formats. The UKB imaging data were reviewed in NIFTI format, using MRIcron imaging viewer software programme (Neuroimaging Tools and Resources Collaboratory, University of South Carolina, v1.0.20190902, 2019) (201). It is a stand-alone freeware (under the BSD licence) used for viewing brain images in NIFTI and DICOM formats. The MRICron software was installed onto the UCL remote working station. The same display monitor (LG UltraFine 4K, 2019, as used for the QUASARS study) was used by the researcher to view the images remotely, in semi-dark conditions. The images were viewed using the slice viewer panel, with default

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values for window centre (image intensity) and window width, as set out by the UKB, and with auto-contrast setting to allow standardised viewing of the imaging.

SWI	3D dual-echo gradient echo (GRE) sequence TE1=9.4ms, TE2=20ms, TE=27ms and an in-plane acceleration factor of 2 Field of view: 256x288x48 matrix Resolution: 0.8x0.8x3.0 mm
T2-weighted FLAIR	T2-weighted MRI: Fluid-attenuated inversion recovery (FLAIR) protocol (3D SPACE) TI = 1800ms, TR = 5000 ms and an in-plane acceleration factor of 2 Field of view: 192x256x56 matrix Resolution: 1.05x1.0x1.0 mm
T1-weighted	T1-weighted MRI: 3D MPRAGE protocol TI = 880 ms, TR = 2000 ms and an in-plane acceleration factor of 2 Field of view 208x256x256 matrix Resolution 1.0x1.0x1.0 mm

Table 2.1. UK Biobank MRI acquisition protocols. Reproduced under Creative Commons CC BY 4.0 International license, from Wang et al, 2022 (200).

2.4.4 Equipment for QoL in iSS and ARHL Study

The UCL-licenced REDCap platform was used to deliver the survey. To set up the survey, the REDCap platform was accessed remotely from a dedicated UCL encrypted machine using institutional login credentials and password. The survey was set up to include three parts (sections): (1) study-specific questions; (2) generic HRQoL questionnaires; (3) hearing-specific questionnaires. The questionnaires included in the survey are described below.

2.4.4.1 Generic HRQoL questionnaires

1. Health Utilities Index Mark III (version: English language, 1-week recall), HUI3

2. EQ5D EuroQoL-5D-5Level (version: REDCap, English language; 1-week recall), EQ5D

2.4.4.2 Hearing-specific questionnaires

3. Modified Amsterdam Inventory for Auditory Disability and Handicap (mAIADH)

4. Speech, Spatial and Qualities of hearing scale (SSQ)

5. ERSA Evaluation du Retentissement de la Surdité chez l'Adulte: evaluation of the impact of hearing loss in adults (ERSA)

6. Tinnitus Functional Index (TFI)

2.5 Methods

2.5.1 AViSS Study

When assessing the audiovestibular function, the test choice depends on a number of factors, including test availability, its suitability for the populations in whom it is to be used, the setting and time required to carry out the test, all of which should be taken into account. It is necessary to consider the individual's characteristics, such as age, effort, fatigability, and the presence of contraindication to specific tests or the presence of additional factors that would impede interpretation of the test results. The test choice must also reflect the purpose to identify the site of suspected pathology.

In view of the likely involvement of the central and peripheral segments of the audiovestibular pathway in individuals with iSS, it was, therefore, important to include the tests that assess both peripheral and central audiovestibular function.

The tests described in this work were undertaken at the testing facilities of the Department of Neuro-otology and Audiovestibular Medicine at the Trust, using the departmental clinical audiovestibular equipment described earlier. The tests were performed as part of the clinical care; eleven patients underwent audiovestibular testing as part of the research study. Verbal consent prior to testing was obtained from all the patients and the research study participants. The UCLH Trust and departmental infection control policies including those for COVID-19 were followed.

All the testing was performed in line with the BSA recommendations (202-205). As mentioned earlier, all the equipment had undergone necessary routine and regular interval and pre-test calibrations and checks, performed in line with the current recommendations from the BSA and as per institutional standard operating procedures (202). The normative data for the tests are included in **Appendix 1**.

2.5.1.1 Auditory function tests

The auditory testing was performed in the clinical facility in line with the BSA recommendations (202-204).

PTA was carried out to obtain the hearing thresholds, using pure-tone stimuli presented via headphones and using a calibrated audiometer, in line with the BSA (203). Pure-tone thresholds were used to calculate the threshold averages as follows: three-frequency (3FA) at 0.5/1/2 kilohertz (kHz) and four-frequency (4FA) at

0.5/1/2/4 kHz (206). At the frequencies where the thresholds were not reached, the values of 120 decibel hearing level (dB HL) were substituted. The 3FA and 4FA values were compared to the normative data derived from a large English population sample and were matched for ear (right, left or both), age (in 10-year incremental groups) and gender. Due to the predominantly retrospective nature of the data collection, information about patients' occupation and exposure to noise was not uniformly available. Therefore, the 3FA and 4FA values were not matched for occupational group or noise exposure and instead the reference values for the overall occupational group with noise-exposure (which also includes middle ear involvement with air-bone gap > 10 dB hearing level, HL) were used (206).

Middle ear function was assessed after the PTA and prior to other audiovestibular tests as the middle ear involvement (pathology) would otherwise preclude reliable interpretation of OAEs, ART and ABR test results. The middle ear status for the individuals was verified with a tympanogram (immittance tracing), obtained using a calibrated middle ear analyser with a continuous signal of 226 Hz delivered with an ear-canal probe to each ear separately (204). The tympanometry (immittance) values considered normal as follows: compliance 0.3-1.6 ml, middle ear pressure -50 to +50 dekaPascal (daPa) and ear canal volume 0.6-2.5 cm^3, in keeping with the BSA recommendations (204). The presence of middle ear involvement was excluded if the tympanometry (immittance) results were normal.

The test of otoacoustic emissions (OAEs) was used to determine the cochlear functional status. OAEs measure the response of outer hair cells to sound stimuli (207), and in the presence of normal middle ear function, absent OAEs imply

impairment of outer hair cells (with the type of sensory hearing loss termed as "sensory transmissive") whereas involvement of inner hair cells (termed as "sensory transduction" hearing loss) would demonstrate normal OAEs (207, 208).

Interpretation of OAEs and thus the assessment for the presence of cochlear hearing loss is considered unreliable with pure-tone thresholds of ≥ 30 dB HL; responses can also diminish or become absent with age (209, 210). Distortion product and transient evoked otoacoustic emissions (DPOAEs and TEOAEs) are the most commonly used OAE tests in the clinical setting, and it is recommended by the BSA that both are used (202).

TEOAEs and DPOAEs are performed using linear click stimuli (TEOAEs: 81-87 dB sound pressure level (SPL) intensity and frequency range: 1.0-4.0 kHz; DPOAEs: 55/65 dB SPL and 70/70 dB SPL if poor or "noisy" tracing or if elevated cochlear thresholds of frequency range 0.5-12.0 kHz, delivered with an ear-canal probe and using a dual-channel analyser system (211). Responses are considered diagnostic when 260 sweeps are achieved, and the amplitudes of response are $\geq$ -10 dB SPL. Responses are considered normal if the amplitude responses with signal-to-noise ratio (SNR) of 6 dB or greater are present in 3 or more adjacent frequency bands (212).

Speech audiometry (in quiet) aims to assess the listener's performance to speech stimuli which should improve with increased sound presentation levels (213). A decrease in performance despite an increase in presentation levels is known as a "rollover phenomenon" and may be suggestive of retrocochlear pathology (214, 215). This is particularly useful in instances where the cochlear function cannot be reliably

ascertained and to support the findings of other tests suggestive of retrocochlear involvement.

The speech audiometry test is performed after the PTA hearing thresholds are recorded. It includes a pre-recorded Arthur Boothroyd (AB) isophonemic monosyllabic word list (of up to 30 words, presented in 10-word lists) (215). The words follow the consonant sound-vowel sound-consonant sound pattern and are presented in isolation via headphones.

Speech discrimination score was obtained and plotted on a performance intensity graph. An interaural difference of 20-30% in scores or presence of a "rollover" effect (rollover ratio of > 0.4) is considered significant for retrocochlear pathology (215-217). The rollover ratio is calculated using the following formula:

$$Rollover\ ratio = \frac{PBmax - PBmin}{PBmax}$$

where PBmax and PBmin are is the highest and lowest speech discrimination scores, respectively (217).

The departmental reference values for maximum speech audiometry percent discrimination scores consistent with PTA thresholds are: 100%, 75%, 50% and 25% for normal/mild, moderate, severe and profound degrees of sensorineural hearing loss, respectively. Speech discrimination scores which were worse than expected for PTA thresholds were suggestive of cochlear nerve involvement (218).

To assess for the presence of lesions involving auditory brainstem nuclei and determine the auditory nerve function, two tests (or both) can be used (18, 219-221).

These include testing of acoustic reflex thresholds (ART) and auditory brainstem responses (ABR) (18, 219, 220). ART response can be ipsilateral or contralateral. The ipsilateral ART response is elicited by activating the stapedial reflex arc, with the afferent component travelling along the auditory (cochlear) nerve of the CNVIII and synapsing in the cochlear nucleus in the brainstem (222). The impulse then synapses with the ipsilateral facial nerve nucleus and is carried by the facial nerve (CNVII) which innervates the stapedius muscle (the efferent pathway) and elicits the ipsilateral response. The contralateral response is characterised by the impulse travelling from the ipsilateral cochlear nucleus to the trapezoid body and to the superior olivary complex in the brainstem, and crossing over to the contralateral facial nucleus and then traveling along the contralateral facial nerve (223).

ART is performed using a middle-ear analyser with the stimuli presented monaurally at 0.5/1/2/4 kHz and responses recorded ipsi- and contra-laterally. The reflex is considered present when the middle ear compliance change of ≥ 0.03ml is recorded. In this project, acoustic reflex thresholds were compared against the 90th percentile values for the contralateral thresholds (0.5/1/2 kHz) (213, 224) The responses were considered abnormal if, for least 2 adjacent frequencies, the reflex was not recorded at > 100 dB HL or if interaural threshold difference of > 10 dB was present (220). The status of middle ear was recorded.

	EAR		
Test site	Right	Left	Likely lesion site
ipsi	Elevated	✓	Middle ear
contra	✓	✓	
ipsi	Elevated	✓	Cochlea
contra	Elevated	✓	
ipsi	Absent	✓	Auditory nerve
contra	Absent	✓	
ipsi	Absent	✓	Facial nerve
contra	✓	Absent	
ipsi	✓	✓	Brainstem (small intra-axial lesion)
contra	Absent	Absent	
ipsi	Absent	Absent	Brainstem (large intra-axial lesion)
contra	Absent	Absent	

Table 2.2. Patterns of acoustic reflex thresholds (ART) findings and respective site (level) of pathology, given for right-sided lesion (adapted from Cohen and Prasher, 1988) (220). Legend: ipsi – ipsilateral, contra- contralateral, ✓ ART present.

ART has been used in assessments of intra-axial brain lesions and multiple sclerosis (219, 225, 226). Several limitations, however, are associated with the test. It can, for example, be limited by the presence of severe-to-profound hearing loss and it does not identify which part (distal/middle/proximal section) of the auditory (cochlear) nerve is affected (227). It is, therefore, important to include another measure that would complement the assessment of auditory nerve function (220).

ABR test should be included in the test battery alongside ART testing as the combination of two tests allows to assess disease-specific patterns in neuro-otological disorders (220). ABR allows the assessment of auditory nerve function and neural activity from cochlear spiral ganglion to the auditory brainstem nuclei (221, 228). It comprises five waves, with each wave representing a segment of the auditory nerve (228, 229):

Wave I – distal portion of the cochlear nerve;

Wave II – proximal portion of the cochlear nerve;

Wave III – cochlear nucleus;

Wave IV – lateral lemniscus;

Wave V – inferior colliculus.

ABR were recorded through amplified and filtered electrical activity using a multi-channel Evoked Potential System recorder. Three electrodes (one each, and of impedance <5 kOhm) were placed on the forehead (common) and each mastoid (ipsilateral positive, contralateral negative) of the individual being tested. Monaural alternating click stimuli (range 2-4 kHz, 100 μsec duration and a total number of 1000 stimuli) were presented via TDH-headphones at a rate of 11.1 per sec and minimum intensity of 90 dB HL. The test was performed twice to minimise the risk of error. The activity traces were recorded and the measurement values for Wave I, III, V peak wave latency and inter-wave latency intervals were obtained and compared with the institutional normative data **(Appendix 1)**. Wave morphology was also reviewed. ABR was considered abnormal in the presence of (1) poor wave

morphology; (2) poor repeatability of responses; (3) one or more waves were absent; or values were outside of the departmental normative values for: (4) peak latency for at least one of the waves (Wave I, III, V), or (5) inter-wave latency (I-III, III-V, I-V) (17). ABR test was deemed inconclusive if pure-tone thresholds of ≥ 70 dB HL at 4 kHz or the average of both 2 and 4 kHz was ≥ 70 dB HL, or the 1 and 4 kHz slope was > 40 dB HL (230).

Central auditory pathway from the brainstem nuclei to auditory cortex was assessed using several tests. The tests were performed as part of the clinical care or in the research setting (AViSS study). The two main tests were used to assess central auditory function: Listening in Spatialized Noise-Sentences (LiSN-S) test and Quick Speech-in-Noise (QuickSiN) test.

The LiSN-S test assesses the listener's segregation skills from a stream of auditory stimuli in a three-dimensional testing environment (231). It can be used as a tool to assess for the auditory as well as spatial processing deficits. The test can be adjusted to the listener's hearing levels based on the listener's PTA thresholds recorded prior to the LiSN-S test. The test (North American version) was performed using Phonak software programme and USB Phonak soundcard. The stimuli (target sentences of 5-7 words) were presented to the listener through Sennheiser headphones at the azimuth direction (0 degrees = 0°). The competing/masking sentences were presented simultaneously to both ears at different or same pitch to the target stimuli and at 90 degrees (90°) or 0° to the azimuth, thus creating four potential conditions (domains): (1) high cue: the competing/masking stimuli presented at 90° and different pitch to the target stimulus at the azimuth; (2) spatial

advantage: the competing/masking stimuli presented at 90° and same pitch as the target stimulus at the azimuth; (3) talker advantage: the competing/masking stimuli presented at 0° but different pitch to the target stimulus at the azimuth; (4) low cue: the competing/masking stimuli presented at 0° and same pitch to the target stimulus at the azimuth (231). The correct responses were recorded for each sentence or part thereof. The scores were calculated automatically by the software, for each domain and as a total score. It was indicated by the software if the recorded scores were below the expected norms (232).

The QuickSiN (Etymotic Research, IL) test is a short speech recognition threshold-in-noise test which is considered a quick screening measure for central auditory processing deficits (233). It is considered as part of the central auditory processing test battery because it allows to estimate listener's hearing thresholds – represented by signal-to-noise ratio (SNR) loss – in the presence of the background noise (of four-talker babble) (233). In QuickSiN, central auditory processing deficits may be considered present when the SNR loss values are markedly worse than the hearing thresholds (233). The test was performed using the pre-installed software with the test stimuli presented through TDH headphones at 70 dB HL if PTA average thresholds were ≤ 45 dB HL; the stimulus was increased to 80 dB HL presentation level in the presence of elevated (> 45 dB HL) PTA average thresholds (234). A minimum of two lists of six sentences with five key words were presented to the listener with the SNR decreasing from 25 dB to 0 dB in increments of 5 dB and thus increasing the difficulty of the test. The SNR loss (in dB) was calculated based on 50% correct responses and was categorised as follows (for normal hearing individuals with hearing thresholds ≤ 20 dB HL across 0.25 to 8 kHz): normal/near

normal 0-3 dB, mild 4-7 dB, moderate 8-15 dB, severe > 15 dB (233, 234). For individuals with the hearing thresholds of > 20 dB HL across 0.25 to 8 kHz, the SNR loss > 2.75 dB than the higher end of the value range for normal hearing subjects was considered abnormal (233).

2.5.1.1.1 Interpretation of auditory test results

Cochlear (pre-neural) involvement was considered in the presence of mildly elevated thresholds, normal tympanometry and normal ABR, elevated speech discrimination scores without the "rollover" phenomenon and/or abnormal otoacoustic emissions (202-204).

Retrocochlear involvement was considered in the following cases:

a. at the neural or brainstem (or both) levels: in the presence of normal/elevated pure-tone thresholds (≤70 dB at 2.0 and 4.0 kHz), the presence of otoacoustic emissions, normal tympanometry, abnormal ART and/or ABR and/or presence of "rollover" on speech perception audiometry (235).

b. at the level of the auditory cortex (central auditory deficits/impairment): in the presence of abnormal central auditory processing tests, with normal ABR findings and ART pattern.

c. at the neural, brainstem, auditory cortex level (mixed pattern of involvement): in the presence of both auditory processing and low brainstem test abnormalities.

The following additional risk factors for hearing loss were identified in the study cohort. They were considered during the case-by-case evaluation and interpretation

of the auditory findings to determine the likely affected segment along the auditory

pathway **(Table 2.3)**.

Risk factors as possible secondary causes for hearing impairment	Likely segment affected	Reference
Head trauma from road and cycling accidents	Cochlear, retrocochlear	(236)
Posterior fossa surgery including foramen magnum decompression for Arnold Chiari malformation	Retrocochlear	(237-241)
Posterior fossa radiotherapy	Cochlear, retrocochlear	(242)
Meningitis, encephalitis	Cochlear, retrocochlear	(243-246)
Hydrocephalus	Cochlear, retrocochlear	(241, 247)
Unrecovered idiopathic sudden sensorineural hearing loss	Cochlear, retrocochlear	(248, 249)
Spontaneous low CSF pressure	Cochlear, retrocochlear	(241, 250)
Familial early onset hearing loss	Cochlear, retrocochlear	(251)
Posterior circulation stroke	Cochlear, retrocochlear	(252-254)
Noise-induced hearing loss	Cochlear, retrocochlear	(255)
Meniere's disease (endolymphatic hydrops)	Cochlear	(256)
Congenital sensorineural hearing loss	Cochlear, retrocochlear	(251, 257)
Diabetes mellitus	Cochlear, retrocochlear	(258)

Table 2.3**.** Risk factors as possible secondary causes for hearing impairment, as
identified in some individuals in the AViSS study cohort.

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2.5.1.2 Vestibular function tests

All vestibular tests were carried out in the clinical facilities, as described earlier. All

testing equipment was calibrated in line with the manufacturers' instructions, the

BSA recommendations and departmental standard operating procedures (202, 205,

259, 260).

The function of all six SCCs can be assessed using the video head impulse test

(vHIT). It allows to evaluate the slow phase eye movements as a response to high-

velocity passive head movements and measure the vestibulo-ocular reflex (VOR).

The presence (or absence) of the corrective saccadic (CS) eye movements, which

are the compensatory re-fixating saccadic eye movements, can be recorded. They

can be covert or overt, differentiated by their timing. Covert saccades occur during

the high-frequency head impulses whereas overt saccades occur after such head

impulses (261).

The vHIT test was performed using ISC impulse monocular (right-eye) infra-red

video oculography system (Otometrics, Natus Hearing and Balance Group) (259).

The individual was asked to focus on a vertically fixed point placed centrally at the

individual's eye level at one metre in front of him/her. The head and eye movements

were recorded with the video oculography system, during a brief sudden and

unpredictable (10-20˚ angle) head turns (impulses) in the planes of the semicircular

canal pairs being tested: (1) right and left lateral (or horizontal); (2) left anterior and

right posterior (LARP); and (3) right anterior and left posterior (RALP). The minimum

peak head velocities required for accurate interpretation of the test were for lateral

impulses: 120˚/sec, acceleration 1200˚/sec^2, and for LARP/RALP: 100˚/sec,

acceleration 1000˚/sec^2, with bilaterally similar velocity and acceleration, and not

exceeding 250°/sec and 2500°/sec^2, respectively (259). A minimum of 20 impulses

for each canal was recorded (262). The VOR gain was calculated by the software

and is represented as the area under the curve between the head and VOR eye

velocity (259). The eye movement recording was assessed for the presence of CS,

and, if present and were deemed consistent, their (CS) latency, direction and

amplitude were assessed (263). The individuals were assessed for the presence of

contraindications prior to testing. The contraindications to testing included

poor/limited or painful neck movement, history of recent cranial or spinal surgery,

hydrocephalus (with or without VP shunting), low CSF pressure, recent head trauma,

abnormal right eye movements or the presence of cranial nerve III, IV, VI palsies,

Horner's syndrome or significant ptosis that would interfere with the eye-movement

recordings.

The test was considered normal in the absence of abnormal CS (defined below) and

the VOR gain values falling within the normal ranges values provided by the

manufacturer, based on the their collected research data) which were: 0.8-1.2 for

lateral (horizontal) plane impulses, and 0.7-1.2 for RALP/LARP planes impulses

(259, 264). The presence of repeatable (consistent) CS (overt/covert) was

considered abnormal if their amplitude was half or greater of the peak head velocity

amplitude, or the onset of CS was between 100-250 msec after the onset of the

head movement, and irrespective of the VOR gain; the findings were further

strengthened (interpreted as abnormal) if the VOR gain was outside of the normal

range for the canal tested (264). Ambiguous cases, including cases with abnormal

VOR gain without abnormal CS were discussed with at least one senior clinician.

The presence of saccadic eye movements which appeared in opposite direction to the head movement was considered to be due to nystagmus.

Caloric test assesses lateral (horizontal) canal function and its afferent pathways (263). Excitatory and inhibitory responses in the form of nystagmus are observed during the test, and the direction, amplitude, speed of the slow component or duration of nystagmus are recorded (22). Canal paresis (CP), directional preponderance (DP) and visual fixation index (VFI) (normal <50%) were calculated as part of the caloric testing by measuring slow phase eye velocities (23).

The departmental procedure for caloric testing which followed the BSA recommendations (260) and involved the use of bithermal water caloric irrigation system **(Appendix 1)**, with water temperature 30° ± 0.4° and 44° ± 0.4° for warm and cool water testing, respectively. The irrigation volume of 250 ± 10 ml was delivered in 30 sec, and each ear was irrigated twice (260). The eye (pupil) movements were recorded using the binocular infra-red video-nystagmography (VNG) eye tracking system (monocular recordings were performed in the presence of dysconjugate eye movements); or by measuring corneoretinal potentials using electronystagmography (ENG) system **(Appendix 1)**. The individual was placed in supine position with a 30-degree (30°) angle elevation. Prior to testing, the individual was assessed for contraindications to the test including acute vertigo or dizziness, tympanic membrane perforations or abnormal middle ear status (abnormal tympanometry/immittance results or abnormal findings on otoscopy suggestive of middle ear involvement or presence of a tympanic membrane perforation), presence of otitis externa or significant amount of wax in the external auditory canal, recent history of ear or eye surgery, history of epilepsy, uncontrolled hypertension or

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significant cardiac disease, pregnancy, ingestion of alcohol or prochlorperazine 48

hours prior to testing (204). Warm water irrigation was carried out first (without the

preference to the right or left ear), in line with the BSA recommendations (260). If

monothermal caloric weakness was identified on warm-water testing, (departmental

reference >10%), the cool water testing was then carried out, otherwise the test was

deemed complete with the findings of "no abnormality detected". Values for the canal

paresis (CP) was calculated using Jongkees equation, as follows (265):

$$\text{CP (\%)} = \frac{(Warm\ Right + Cold\ Right) - (Warm\ Left + Cold\ Left)}{Warm\ Right + Warm\ Left + Cold\ Right + Cold\ Left} \times 100$$

Directional preponderance (DP) was calculated using the following formula (260):

$$\text{DP (\%)} = \frac{(Warm\ Right + Cold\ Left) - (Warm\ Left + Cold\ Right)}{Warm\ Right + Warm\ Left + Cold\ Right + Cold\ Left} \times 100$$

Abnormal results on caloric testing (CP and DP) were indicated if outside of the

institutional normative values **(Appendix 1)**. Abnormal caloric testing results

obtained from clinic letterswere referred to as "hypofunction".

The functions of otolith organs (utricle and saccule) and respective superior and

inferior vestibular nerves were assessed by measuring ocular and cervical vestibular

evoked myogenic potentials (oVEMP and cVEMP) of the contralateral inferior

oblique muscle and the ipsilateral sternocleidomastoid muscle, respectively (266,

267). While the cVEMP assesses the ipsilateral sacculocollic reflex pathway, the

oVEMP stimulus pathway (between superior vestibular nerves and the (contralateral)

inferior oblique muscles) includes the stimulation of ipsilateral utricle and superior

vestibular nerve and contralateral vestibular nuclear complexes, medial longitudinal fasciculi, oculomotor nuclei and oculomotor nerves (268).

VEMPs can be affected by age, and therefore bilaterally absent responses or reduced wave amplitudes were considered equivocal in patients aged ≥ 60 years, due to likely age-related changes affecting the vestibular system rather than the tonus of the sternocleidomastoid (269-271).

Prior to testing, the patients were assessed for contra-indications to the test which included presence of conductive hearing loss or middle ear dysfunction (including abnormal tympanometry results), intolerance to loud sounds, presence of dysconjugate eye movements or inability to look up or maintain up-gaze (oVEMP) or neck problems (cVEMP). In patients with percutaneous ventriculo-peritoneal shunting, use of inserts was indicated.

The oVEMP and cVEMP tests were undertaken using a multi-channel evoked potentials system, as described in Section 2.4.1.1. Three electrodes of impedance <5 kOhm and not exceeding 15 kOhm, were placed (one each) on the forehead (common) and over contralateral inferior oblique/cheek areas (positive/negative, for oVEMP) and over ipsilateral sternocleidomastoid/sternum areas (positive/negative for cVEMP) to record ocular and cervical myogenic potentials, respectively.

For oVEMP testing, sound stimuli (tone bursts, stimulus level 115 dB SPL) were used whereas for cVEMP testing, pip (2-1-2) sound stimuli were presented at 105 dB normalised Hearing Level (nHL). The stimuli were presented via TDH headphones at 0.5 kHz frequency to one test ear at a time (for either oVEMP or cVEMP).

The signals between 60 and 80 µV were recorded and their averages were

calculated. Responses were considered present if responses in the format of two

waves (N10 and P15 for oVEMP; P13 and N23 for cVEMP) were identified on the

traces. Each side was tested twice to minimise the risk of error. For oVEMPs, the

responses were assessed whether present or absent, and if present, the inter-aural

asymmetry of the wave amplitudes, as well as the threshold levels were compared

with the departmental normative data **(Appendix 1)**. For cVEMPs, the responses

were assessed whether present or absent. If present, the responses were assessed

for threshold levels and asymmetry in the thresholds and amplitudes, latency values

for P13 and N23 as well as P13 and N23 interaural difference limits; these values

were then compared with the departmental normative data for cVEMPs **(Appendix

1)**.

Oculomotor function and rotation chair testing assess central and peripheral

vestibular function, using VNG, or ENG eye tracking systems which allow to record

the eye movements during testing either with the infra-red eye-tracking camera or by

measuring the corneoretinal potentials, respectively. Oculomotor testing involves

assessment of saccadic eye movement, smooth pursuit, optokinetic nystagmus, as

well as the assessment of gaze for presence of nystagmus (spontaneous, gaze-

evoked/directional, with or without fixation). Rotation chair assessments include

sinusoidal harmonic acceleration rotational testing (measures the patient's VOR by

recording nystagmus as a response to the rotating chair change of direction, and

measuring gain and phase of the response), VOR suppression (tests the patient's

ability to suppress nystagmus following from the SHA testing) and impulsive (step)

rotation testing.

The oculomotor testing was performed in a darkened room and the rotation chair tests were performed in complete darkness, using one of the VNG or ENG systems, as described in Section 2.4.1.3.

The oculomotor eye movements were assessed as follows:

a. Saccadic eye movement was tested at 0 (0°) and 20 degrees (20°), in right/left directions;

b. Smooth pursuit was tested at 0.2/0.3/0.4 Hz;

c. Gaze was tested at 0° and 20°, in four directions: right, left, up-gaze, down-gaze;

d. Optokinetic nystagmus was tested at 15°/sec and 35°/sec, in clockwise and counter-clockwise directions;

e. Sinusoidal harmonic acceleration rotation test was performed at 0.08 Hz, 60°/sec (for VNG) or at 0.2 Hz, 40°/sec (for ENG); responses were considered inconclusive if excessive noise (eye movements) was recorded on the traces and if in the presence of gaze abnormalities.

f. VOR suppression was tested with the same test parameters as for sinusoidal rotation while the individual fixating on a light;

g. Impulsive (step chair) rotation testing was performed with acceleration impulse of $100°/sec^2$ to a fixed chair velocity in right/left directions.

2.5.1.2.1 Interpretation of vestibular test results

The following criteria were used to identify the likely site of vestibular impairment. Unilateral peripheral vestibular involvement was indicated by the presence of at least one of:

a. Unilateral canal paresis on caloric testing in the absence of optic fixation (265, 272);

b. Unidirectional spontaneous horizontal nystagmus (>4°/sec for ENG testing or (>3.75°/sec for VNG) enhanced without optic fixation on gaze testing. (273).

c. Asymmetry >15% in slow-phase velocity (SPV) between right and left step rotation testing (265);

d. Asymmetry in sinusoidal harmonic acceleration (SHA), further corroborated by findings suggestive of unilateral peripheral vestibular hypofunction, such as identified on caloric testing;

e. Unilaterally absent or asymmetrical or abnormal (outside of the norms) cVEMP/oVEMP responses in the presence of other ipsilateral peripheral vestibular deficits as identified by other tests, such as on vHIT testing: unilateral VOR gain deficit with ipsilateral large amplitude CSs (inversely mirroring VOR gain reduction), or significantly unilaterally reduced VOR gain with bilateral CSs of large amplitude (inversely mirroring VOR gain reduction) (262); or ipsilateral canal paresis as identified on caloric testing, or confirmed asymmetry suggestive of ipsilateral weakness on step rotation testing, as described above.

Bilateral peripheral vestibular involvement was indicated by at least one of:

a. values of > 2 standard deviations (SD) than normal population means on oculomotor testing using step rotation testing in:

- slow phase eye velocity component (normative mean 32°/s, SD 8°/s);

- time constant (normative mean: 13.35 sec, SD 4.45 sec) (274);

b. reduced gain on sinusoidal harmonic acceleration testing;

c. caloric responses: bilaterally absent;

d. vHIT testing: bilaterally and symmetrically reduced VOR gains with bilateral CSs of large amplitude (inversely mirroring VOR gain reduction), (262, 275);

e. bilaterally absent or abnormal (outside the normative values) cVEMP/oVEMP responses deemed not due to age (< 60 years old).

Central vestibular involvement was indicated if at least one of the following was abnormal on oculomotor or rotation chair testing, i.e., the measurements falling outside the departmental norms for ENG **(Appendix 1)** or outside the manufacturer's norms for VNG (276):

a. Presence of gaze abnormalities such as vertical nystagmus (downbeat or upbeat or both), or direction (gaze)-changing nystagmus present or enhanced with fixation; or presence of abnormal square waves (if the frequency of square waves was > 30/min) or ocular flutter;

b. Abnormal smooth pursuit;

c. Abnormal saccadic eye movements such as abnormal accuracy (hyper- or hypometric saccades), or abnormal velocity, or abnormal latency;

d. Reduced gain on optokinetic nystagmus;

e. Abnormal vestibulo-ocular reflex suppression;

f. Abnormal (increased) gain in the presence of other central vestibular features and in the absence of other peripheral vestibular features.

g. Inability to suppress caloric nystagmus on caloric testing.

Central vestibular involvement was considered on vHIT (262, 277-279) in the presence of at least one of the following:

a. Bilaterally symmetrically reduced VOR gains recorded with CSs of small/minimal amplitude;

b. Bilaterally symmetrically reduced VOR gain, with the asymmetry in amplitude of ipsilateral and contralateral CSs (in contrast to the highly asymmetrical VOR gains with corresponding CSs of large amplitude for unilateral peripheral lesions);

c. Bilaterally reduced VOR gains involving lateral (horizontal) SCCs and sparing of both anterior and posterior SCCs (indicated by their normal VOR gains), and the presence of CSs not correlating with the VOR gain reduction, which may be suggestive of cerebellar involvement;

d. Bilaterally reduced VOR gains involving lateral (horizontal) and posterior SCCs, with anterior SCC sparing, in the presence of other central oculomotor signs such as bilateral directional gaze-changing nystagmus with fixation (which would differentiate it from peripheral bilateral vestibulopathy with anterior SCC sparing suggestive of the involvement of the vestibular nuclei;

e. Presence of reverse saccades (which are in the opposite direction to the head movement likely due to the central/up-beat nystagmus), with reduced VOR gains;

f. Increased VOR gains on lateral (horizontal) SCC testing, accompanied by the reversed CSs, defined as "saccades generated in response to increased VOR gains" (278).

Decreased VEMP wave amplitudes, or abnormal or absent waves have been reported in brainstem lesions and in cases of cerebellar lesions with brainstem involvement (268, 280, 281). Therefore, central vestibular involvement was considered on VEMP testing in the absence of responses or if abnormal latencies (with or without reduced amplitudes) were identified, and corroborated by the

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presence of other central vestibular findings in the absence of peripheral vestibular

dysfunction indicated on other vestibular tests.

Presence of additional risk factors for vestibular dysfunction were identified in the

study cohort which are listed in **Table 2.4**. These risk factors were considered during

the interpretation of the findings to determine the likely affected segment along the

vestibular pathway.

Risk factors as possible secondary causes for vestibular impairment	Likely segment affected	Reference
Head trauma from car or cycling accidents	Central, peripheral	(282, 283)
Posterior fossa surgery including foramen magnum decompression for Arnold Chiari malformation or radiotherapy	Central, peripheral	(283)
Meningitis, encephalitis	Central, peripheral	(283, 284)
Hydrocephalus	Central, peripheral	(250)
Spontaneous low CSF pressure	Central, peripheral	(250)
Posterior circulation stroke	Central, peripheral	(26)
Meniere's disease (endolymphatic hydrops)	Peripheral	(285)
Diabetes mellitus	Central, peripheral	(286, 287)

Table 2.4**.** List of risk factors identified in the study cohort and were considered as

possible secondary causes for vestibular impairment.

2.5.1.3 Smell identification test

The University of Pennsylvania Smell Identification Test (UPSIT) was used to test

olfactory function. It is a forced-choice 40-item test that contains four booklets with

strips of embedded microencapsulated odours which are released by scratching the strips with the tip of a pencil supplied with the test kit. The test can be self-administered or administered by a proxy. The scores are calculated as the sum of correct answers, to the maximum best of 40. Correct responses were determined using the answer key provided by the manufacturer (199). Participants' smell test scores were compared to the normative data, stratified for sex and age in 5-year age groups and percentiles recorded (199).

2.5.2 QUASARS Study

2.5.2.1 Development of the QUeen squAre infratentorial superficial Siderosis Anatomical Rating Scale (QUASARS)

The rating scale **(Figure 2.1)** was developed in collaboration and in consensus with the Neuroradiology and Clinical Neurology senior team members who are also the members of the Superficial Siderosis multidisciplinary team at the National Hospital for Neurology and Neurosurgery, Queen Square (London) and in which the researcher (NK) participated as a coordinator. The rating scale was based on the previously described radiological diagnostic criteria for iSS (7).

The scale includes anatomical areas (regions) of the surfaces along which haemosiderin deposits have been previously observed and includes both infratentorial and supratentorial regions **(Figure 2.1)** (7). The following infratentorial regions were included in the scale (in caudal to cephalad sequence): craniocervical junction, cerebellum (cerebellar folia and superior vermis, one region each), 8th cranial nerves (CNVIII), brainstem (medulla, pons, ventral and dorsal midbrain, one region each).

This granular approach to determine involvement of the sub-regions of cerebellum (cerebellar folia and superior vermis) and brainstem (medulla, pons, and ventral and dorsal aspects of midbrain) was deemed necessary by the group to extend the score range and reduce possible ceiling effects. The 8th cranial nerves (CNVIII) were included since hearing loss is almost invariable in iSS (8).

The supratentorial involvement was considered if haemosiderin was visualised along the convexities of at least one or part of the cerebral lobes of the following supratentorial regions: cerebral convexities of the frontal, temporal, parietal and occipital lobes, whether lateral or medial (one region each). Medial involvement of the cerebral lobes was included to reflect their likely involvement of the surfaces of the interhemispheric fissures and other areas where haemosiderin has been previously observed such as medial temporal and medial occipital regions, as well as Sylvian fissures and orbito-frontal regions (one region each) (7).

Sylvian fissure is another key structure of the auditory pathway and its involvement, together with the involvement of the CNVIII, may correlate with the presence of hearing dysfunction (43). Similarly, the involvement of orbito-frontal area may correlate with the symptoms of hyposmia or anosmia suggestive of olfactory (CNI) involvement (7, 64).

Imaging of the whole spinal cord was not included into the rating scale despite it being part of the radiological diagnostic criteria. This was because the spinal imaging might not be available for all patients at the time of their evaluation. Involvement of the spinal cord is, however, represented by the cranio-cervical junction (CCJ), although CCJ might not uniformly reflect the involvement of the spinal cord.

A. Craniocervical junction level

B. CNVIII and medulla level

C. Pons level

D. Orbito-frontal region and midbrain level

E. Sylvian fissures and midbrain level

F. Frontal and parietal convexities level

Patient ID: _____

MRI Date: _____ MRI Sequence: _____

The Queen Square Superficial Siderosis Rating Scale includes 18 regions, for which the presence of a rim of low signal intensity (SWI, T2*GRE or T2-weighted MRI) along the brain surface is rated. Each region is assigned a single point for right/left side involvement, giving a maximum total of 36 points.

Haemosiderin visualised				
Infratentorial structures (DIAGRAM)			**Right**	**Left**
Craniocervical junction (A)				
Cerebellum	*Folia* (B, C)			
	Superior vermis (C-E)			
‡CNVIII complex (B)				
Brainstem	*Medulla* (B)			
	Pons (C)			
	Midbrain (D, E)	ventral		
		dorsal		
‡Supratentorial structures			**Right**	**Left**
Orbito-frontal region (D)				
Sylvian fissure (E)				
Convexity	Frontal (E, F)	medial		
		lateral		
	Parietal (F)	medial		
		lateral		
	Temporal (C-E)	medial		
		lateral		
	Occipital (C-E)	medial		
		lateral		
		TOTAL		/36
†*Spinal cord* involvement (if imaging available)			Y/N	

‡Not part of diagnostic criteria
†Not included in the score, not shown on diagram

CF	Cerebellar folia	Pm	Parietal lobe (medial)
Fl	Frontal lobe (lateral)	Pl	Parietal lobe (lateral)
Fm	Frontal lobe (medial)	SF	Sylvian fissure
Ol	Occipital lobe (lateral)	Tm	Temporal lobe (medial)
Om	Occipital lobe (medial)	Tl	Temporal lobe (lateral)
OF	Orbito-frontal region		

Figures A-F: Schematic representation of cranial structures which may be involved in iSS, at various levels: infratentorially (A-D) and supratentorially (E-F). A. Level of craniocervical junction (black); B. Level of cerebellopontine angle (CPA) and 8th cranial nerve (CNVIII), (inlay, shaded), medulla (shaded), cerebellar folia and inferior cerebellar vermis; C. Level of pons (shaded), cerebellar folia and superior cerebellar vermis (white arrow); D. Level of orbito-frontal region (white arrow), midbrain (shaded); E. Level of Sylvian fissure and insula (shaded), midbrain (shaded) and superior cerebellar vermis, including medial aspect of occipital lobe (white arrow); F. Level of frontal and parietal lobes -medial and lateral convexities: frontal medial (black arrow), parietal medial (white arrow).

Recommended MRI sequences (in order of preference): susceptibility weighted images (SWI (calculated SWI or magnitude (MAG)), T2*-weighted gradient recalled echo (T2*GRE), T2-weighted. Please note that axial T2-weighted images are useful to identify the VIII complex and cross reference to T2*GRE or SWI.
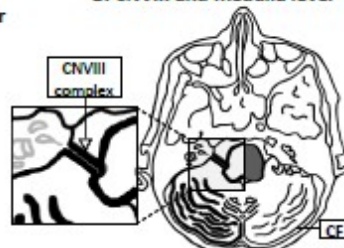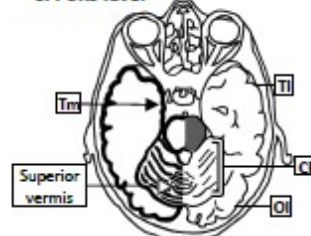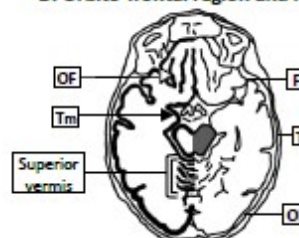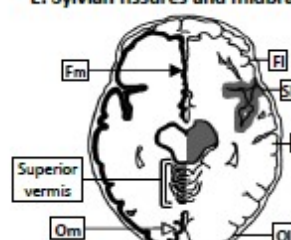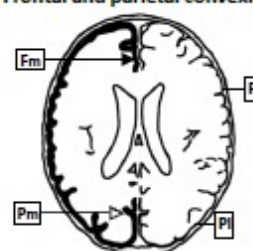
Figure 2.1. QUASARS rating scale proforma.

In total, QUASARS includes 18 anatomical regions on each side (8 infratentorial and 10 supratentorial regions) **(Figure 2.1)**. This is reflected in the score: each region, if involved, is assigned a score of 1, with the maximum score of 8 for the infratentorial compartment and the maximum score of 10 for the supratentorial compartment for each side. Thus, a total maximum score of 18 for each side and 36 (overall, both sides) can be achieved if all the regions demonstrate haemosiderin infratentorially and supratentorially. The difference in scores for right and left sides might reflect asymmetry in visible haemosiderin deposits.

The minimum possible score of zero indicates the absence of any visible haemosiderin on MRI, and probably not compatible with the diagnosis of iSS, at least using susceptibility weighted imaging (SWI). A score of zero might, however, occur on T2-weighted MR imaging which is less sensitive to the presence of paramagnetic substances (69, 71, 288, 289).

Although the radiological diagnostic criteria describe the involvement of minimum two of the infratentorial regions such as the cerebellum, the brainstem or cranio-cervical junction, it has been suggested that involvement of one region such as the cerebellum or superior cerebellar vermis in particular may be observed very early in the course of the disease (7, 14).

2.5.2.2 Imaging acquisition

The MRI sequences were reviewed as part of this study: T2-weighted and paramagnetic-sensitive sequences (T2*GRE or SWI). Both T2-weighted and the paramagnetic-sensitive sequences have been used to visualise haemosiderin

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deposits which appear as a signal loss, albeit with greater sensitivity if paramagnetic-sensitive sequences are used as described in the Introduction chapter (69, 73).

The MR images were acquired at several imaging suites at the Trust, using the institutional imaging acquisition protocols. In some cases, the imaging was performed externally – in the clinical imaging facilities that were most likely local to the patients' home or place of residence. Because imaging was performed at multiple imaging sites and using different MR vendors, the imaging acquisition protocols are not described here. The paramagnetic-sensitive imaging includes T2* gradient-echo (T2*GRE) and susceptibility-weighted sequences (SWI), although different vendors adopted different trade names which include (but not limited to) susceptibility-weighted imaging (SWI, Siemens); SWI with phase enhancement (SWIp, Philips), susceptibility-weighted angiography (SWAN, General Electric Healthcare), flow-sensitive black blood (FSBB, Canon), Gradient Recalled Echo raw data (3D GRE, Philips), blood sensitive imaging (BSI, Hitachi) (291).

2.5.2.3 Imaging viewing

The order of preference in viewing suitable imaging sequences to identify hemosiderin was: SWI, T2*GRE, T2-weighted sequences. All the images were reviewed by the researcher (NK) and where necessary by a co-reviewer, in semi-dark conditions.

To determine the reliability of the rating scale, two raters (researcher and co-reviewer), with different levels of clinical and neuroradiological training and experience (described below), independently reviewed and scored the scans

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simultaneously, in 3 sessions within 3 months. An additional session was necessary to review the imaging (to determine the intra-rater agreement) which took place within 1 month of the previous rating session. The raters were blinded to the patients' clinical data and each other's and own (previous) scores.

Scores were obtained separately for T2-weighted and paramagnetic-sensitive sequences for each MRI study. Brain MR images were reviewed permitting the visualisation of the structures of the CNS to the level of craniocervical junction (CCJ).

2.5.2.4 Quality control procedure

The researcher (NK) received dedicated radiological training from the senior neurology and neuroradiology clinical research team members. The training included detection of the typical appearances of hypointensity (signal loss) areas consistent with superficial siderosis, using T2-weighted and paramagnetic-sensitive MR sequences. The researcher also had a 2-year experience of viewing clinical images of the individuals with iSS as part of the clinical fellow role and the Superficial Siderosis MDT coordinator. The co-reviewer (necessary to determine the rating scale's reliability) was a senior neuroradiology fellow at the Trust and was in the final year of higher specialist clinical training programme in Neuroradiology with the Royal College of Radiologists, UK.

2.5.3 UKB iSS Prevalence Study

Consecutive MR brain images (axial, SWI, with the default windowing standardised by the UKB team) were accessed by the researcher (NK) to identify the presence of

hypointense regions consistent with the iSS pattern of haemosiderin distribution based on pre-defined radiological criteria (7).

2.5.3.1 Imaging data collection and imaging viewing platform

The imaging files were accessed remotely. All the images were viewed by the researcher (NK) in semi-dark conditions.

2.5.3.2 Quality control procedures

As a quality control measure, following completion of the study, the cases with the radiological appearances suggestive of iSS findings were co-verified with the senior members of the research team. The T1-weighted images of the corresponding identified cases were also reviewed to rule out the presence of haemosiderin from previous stroke or focal injury or where signal dropout was suspected to be due to a blood vessel.

2.5.4 <u>QoL in iSS and ARHL Study</u>

The study specific questions and the questionnaires were presented in fixed order. This was done in anticipation of high attrition rates towards the end of the survey, as participants were likely to tire and not complete the survey. Following the confirmation of the study eligibility criteria and after providing informed consent, the participants were taken to the study specific questions **(Appendix 2)**. These included (1) questions on demographic characteristics of the participants, such as age, gender, country of residence, (2) specific questions pertaining to iSS (such as the age at which the diagnosis was achieved, age at which presumed causative event occurred, if known, and whether the participant was in receipt of any treatment and if

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so, whether treatment included medication or surgery or both and the year the treatment had been commenced); and (3) questions regarding hearing (such as whether the participant experienced any hearing difficulties overall and in the presence of background noise, the age of the onset of hearing difficulties, presence of any risk factors for hearing loss, including family history of early onset hearing loss, otological history, hearing levels (if known, and as advised by the healthcare practitioner), use of hearing assistive devices, and whether tinnitus was present, and if so, its severity). All participants were asked if English was their first language.

Following the study-specific questions, the participants were then taken to the pages containing the generic HRQoL (EQ5D, HUI3) and the hearing-specific questionnaires. The parameters of the instruments' are summarised in **Table 2.5**.

2.5.4.1 Generic HRQoL questionnaires

EuroQoL 5D (EQ5D) assesses HRQoL in five domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each domain is represented by a number corresponding to the perceived problem category. A total of 3125 unique health-states can be derived from the combinations of the categories and the domains, which can also be represented in the unique 5-digit health state code for each participant (163). The measured outcomes include respondent's self-perceived health-state represented using a visual analogue scale (as a number from 0 to 100 as "worst - best imaginable" health-state) and multi-attribute (index) utility scores derived from dedicated country-specific value sets (163). For this project, UK-tariff (crosswalk model) was used to calculate utility scores for EQ5D irrespective of the participants' country of residence (290-292).

	Generic HRQoL questionnaires		Hearing specific questionnaires			
	Health Utilities Index Mark III (HUI3)	**EuroQoL-5D-5L (EQ5D)**	**Modified Amsterdam Inventory for Auditory Disability and Handicap (mAIADH)**	**Speech, Spatial and Quality of hearing (SSQ)**	**ERSA***	**Tinnitus Functional Index (TFI)**
Number of attributes (domains)	8	5	5	3	3 (+1)	8
Single attributes (domains)	Vision Hearing Speech Ambulation Dexterity Emotion Cognition Pain	Mobility Usual activities Self-care Pain Anxiety/depression	Intelligibility of speech: - in quiet - in noise Sound: - detection - recognition - localisation	Speech Spatial Other qualities of hearing	Effect of hearing on: Quality of life Personal life Social life Occupational life	Intrusiveness Sense of control Cognitive effect Sleep Auditory function Relaxation Quality of life Emotional distress
Number of	15	25	28	49	15+5	25

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items						
Outcome measures	Single attribute: - by category - utility score Multi-attribute: - by category - utility score	5-digit health-code Visual analogue scale health-status Multi-attribute index (utility) score	Total score Sub-score for each domain	Total score Sub-score for each domain	Total score /150 Total score /200** Sub-score for each domain	Total score (%) Sub-scores for each domain (%)
Number of possible health-states	972 000	243	n/a	n/a	n/a	n/a
Value range (worst-best)	-0.36 to 1	-0.594 to 1	0-3 (average score) 0 to 84 (sum)	0 to 10	0 to 50 (domain) 0 to 150 (total)*	100 to 0‡

Table 2.5**.** Summary of the parameters of the patient-reported outcome measures used. *ERSA Evaluation du Retentissement de la Surdité chez l'Adulte; ** ERSA sum scores for all four domains (total 200 which included occupational domain) were not calculated as the majority of respondents were retired or not in employment; instead total scores out of 150 were reported; the scores for occupational domain (maximum 50) were reported separately. ‡Note the reversal of the percent score for TFI (from best to worst 0-100%).

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Health Utilities Index Mark III (HUI3) assesses the overall functional status and the

individual's HRQoL in eight domains: vision, hearing, speech, ambulation, dexterity,

pain, emotion and cognition (293). It consists of 15 questions of five to six levels.

Two additional questions ask the respondent to rate their health overall and how the

questionnaire was administered (by proxy or as a self-assessment). One-, two-, four-

week recall, and general state instruments are available. One-week recall instrument

was used in this project (in line with another instrument (TFI) that has one-week

recall property to avoid the respondents' confusion regarding the timeframe of

reference) (295). The data interpretation package was provided by the licensor to

calculate the multi-attribute (the overall score "HRQoL") and single-attribute scores

for each of the eight domains and by categories.

2.5.4.2 Hearing-specific questionnaires

The choice for inclusion of hearing-specific PROMs into this study was based on the

likely characteristics of the potential participants. Difficulty hearing in the presence of

background noise as well as the presence of tinnitus have been reported by the

individuals with ARHL and also by the individuals with iSS (294).

Modified Amsterdam Inventory for Auditory Disability and Handicap questionnaire

(mAIADH) is a hearing-specific PROM that contains 28 items. It assesses hearing

function applicable to a range of everyday listening situations and has been used for

individuals with different types of hearing impairment (295, 296). This questionnaire

has been shown to have good internal consistency, satisfactory reliability and validity

(173). It includes five domains: sound detection, recognition, and localisation, as well

as intelligibility of speech in noise and in quiet (173, 295). Responses are scored

from 0 to 3, with the lower scores denoting greater perceived hearing difficulties (173, 297). The total score is calculated as the sum of all scores, with the maximum best scores of 84; the sub-scores are calculated for each of the domains (as the sum of scores from the questions included in the domains). The total scores or the sub-scores represented as the average have also been described and are reported in this format in this work (170, 173, 297).

Speech, Spatial and Qualities of hearing scale questionnaire (SSQ) is a self-report measure consisting of 49 items which refer to different hearing situations in real life (172). It assesses hearing function in three domains: speech hearing, spatial hearing and (other) qualities of hearing. The scores for each question range from 0 to 10 (from no ability to great ability, respectively). The responses for two questions in are scored as a percentage (0 to 100), are then converted to a respective score by dividing the percent score by 10. A total score is calculated as the average of the scores from all the questions. The average of the scores for the questions within each of the three domains represents the (domain) sub-scores.

ERSA ("Evaluation du Retentissement de la Surdité chez l'Adulte: evaluation of the impact of hearing loss in adults") includes four domains (of five items in each) which describe the impact of hearing on the overall quality of life, personal life, social life, and occupational life. The score for each question is obtained using a visual analogue scale from zero (as the lowest, worst) to ten (as the highest, best) score. The sum of scores is reported out of 150 for retired/non-working respondents and out of 200 for those who are in employment. Higher scores indicate lesser impact of hearing loss on the aspects of life, as described above (171). The questionnaire has

been validated in a French-speaking population; it has been translated by its authors into English however it does not appear to have been validated in an English-speaking population (171).

Tinnitus Functional Index (TFI) consists of 25 questions in eight domains which assess tinnitus intrusiveness, sense of control over it, its impact on cognition, sleep, auditory function, relaxation and quality of life, and the associated emotional distress. It is scored on a scale from 0 (little functional impact) to 10 (great functional impact). The score is calculated as an average of the scores obtained from each question, and then multiplied by 10, so that the overall score lies between 0 and 100 percent (as best and worst outcome, respectively (181).

2.6 Ethics permissions and approvals

2.6.1 AViSS Study

The AViSS study was performed as part of the clinical audit and the permission to undertake the audit was sought and granted by the institutional clinical governance team. The research ethics committee permission was sought for the prospective research study. The study was approved by the NHS Health Research Agency and Health and Care Research Wales (HCRW) Research Ethics Committee on the 9th of August 2019, with further amendment to the protocol approval received on the 6th of February 2020. The study registration number is IRAS ID 255835, REC 19/LO/1162 AM01.

2.6.2 QUASARS Study

This study was performed as part of the service evaluation activity, permission for which was sought from the institutional clinical governance team and was registered with the team prior to commencing the study. Research ethics committee approval was not required.

2.6.3 UKB iSS Prevalence Study

The NHS North-West Multi-centre Research Ethics Committee (MREC) granted the approval for the UKB study (the study registration number is 11/NW/0382). All participants gave consent prior to their participation in the UKB study (298). The UKB Access Committee approved the application for data acquisition and granted the permission to the researcher (as part of the research group) to access the UKB under Application Number 16256. Standardised protocol for data acquisition was followed (190).

2.6.4 QoL in iSS and ARHL Study

The study received approval by the UCL Research Ethics Committee (UCL REC 17413/001) on the 12th of March 2020. Permissions for non-commercial (academic) use of for EQ5D, English language (UK) REDCap version (EuroQOL Group Registration ID 33674) and HUI3 (HUI Inc, Dundas, Ontario, Canada, Version: English language, self-administered, 1-week recall) were obtained before the study was commenced. Permissions to use mAIADH, SSQ, ERSA, TFI were sought from the authors. These questionnaires are referenced accordingly and are used under

the Creative Commons International Attributions licence, with no adjustments made to the instruments at any stage of this project (171-173, 181).

2.7   Ethics amendments

Only amendments to the research (AViSS) study were sought and obtained during the project. The first (minor) amendment to the study protocol was granted on the 6th of February 2020. The change to the protocol included use of saliva collection kit (for DNA collection) instead of venous blood sampling.

Second amendment was made as part of the contingency plan in view of COVID-19 pandemic. To ensure participants' safety, the potential participants were informed that the travel means to and from the testing facilities would be facilitated where possible by means of private transport or taxi (instead of bus or underground public transport services) when in London, and these additional travel expenses would be re-imbursed. The potential participants were also asked to take a return journey by taxi from their homes to the train station (if outside London), with the expenses re-imbursed.

Participants were provided with a set of gloves (latex-free) and a face mask prior to attending the testing facility. To minimise time spent at the testing facility, participants underwent fewer tests than originally proposed and described in the study protocol, and where feasible were communicated with remotely (by post or phone or via email). In view of COVID-19 pandemic, the saliva collection was not performed.

2.8 Statistical analyses

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) Versions 26, 27 and 28 (IBM Corp, Armonk, NY). Participants' characteristics were summarised using descriptive statistics. All non-categorical data were assessed for normality of distribution using Shapiro-Wilk test (p-values > 0.05 confirming the assumption of normal data distribution).

Non-parametric tests were used for the analysis of the data that appeared to violate the assumption of normal distribution. Frequencies and percentages were reported for categorical data. Continuous (and normally distributed) data were reported using mean and standard deviation (SD); median and interquartile ranges (IQR) were reported for non-parametric data.

Student's t-test was used to assess for difference in means between two parameters (groups) with normal data distribution. Where cell count was < 5, Fisher exact was used instead. The alpha level was set at 0.05. Where available (provided by the SPSS programme), the 95% confidence intervals (CI) were reported.

To assess for difference between variables with the data that violated the assumption of normal distribution, non-parametric rank tests were used: Mann-Whitney U test for two independent groups, Kruskal-Wallis for the independent variables with more than two groups and Wilcoxon Signed ranks test if the variables contained paired measures. The distribution of the data between the groups was inspected using population pyramid diagrams; mean ranks of the two groups were reported if the data distribution did not appear to have similar distribution on

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inspection of the pyramid diagrams. Otherwise, the difference in medians was reported.

Non-parametric Kendall Tau-b correlation coefficient was calculated (for sample sizes ≤50 participants) to determine correlation between variables that failed the assumption of normal distribution, with the levels of correlation set as strong $[T_b] \geq$ 0.3; moderate $0.20 < [T_b] < 0.29$, and weak $0 < [T_b] < 0.19$ (299). The use of Kendall Tau-b was chosen over Spearman-Rho correlation coefficient for analyses of groups with small sample sizes (≤ 50), as it has previously demonstrated better suitability for small sample size (300). Non-parametric Spearman Rho correlation analysis was performed for groups with sample size > 50 participants. The Spearman Rho correlation levels were defined as: strong $[r_s] \geq 0.5$; moderate $0.30 < [r_s] < 0.49$, and weak $0 < [r_s] < 0.29$ (301, 302).

Pearson's correlation coefficient was calculated for strength of association for data that were normally distributed (303). The levels of association were defined as: values less than -0.5 or greater than 0.5 as strong; from -0.49 to -0.30 and from 0.30 to 0.49 as moderate and from -0.3 to 0.3 as weak. Linear regression analysis was performed to determine the strength of association and predict the outcomes between several statistical parameters which are described in detail in the methodology sections of the respective chapters.

The prevalence was calculated using the formula below (304, 305):

$$\text{Prevalence (\%)} = \frac{\text{cases identified}}{\text{total number of cases}} \times 100$$

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The 95% CI for prevalence were calculated using Wilson's Score method, available from the Public Health England tool for calculating common public health statistics (304, 306). The calculations were co-verified using the 'OpenEpi Collection for Epidemiologic Calculations' software (v3.01, 2013, Emory University, Atlanta, USA (305, 307).

To maintain the anonymity of the study cohorts in view of rarity of iSS, aggregated age, gender, demographics data were provided where applicable.

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CHAPTER 3   AViSS STUDY

PHENOTYPING OF AUDIOVESTIBULAR FUNCTION OF INDIVIDUALS WITH

INFRATENTORIAL SUPERFICIAL SIDEROSIS

3.1   Introduction

The hallmark of classical iSS are impairments of hearing and balance (8). Our

knowledge regarding the audiovestibular dysfunction in iSS is limited and there is

paucity of dedicated and comprehensive assessments to characterise the

audiovestibular function and determine the likely affected segment along the

audiovestibular pathway (13, 80). The reports describe predominantly retrocochlear

and less frequently cochlear involvement and, central (cerebellar) and peripheral

vestibular involvement (13, 30, 34, 36, 41, 42, 46, 49, 51, 308).

One of the largest cohort of patients with iSS was described by our dedicated clinical

team at the National Hospital for Neurology and Neurosurgery, Queen Square,

London. It included 65 patients with iSS, identified in the presence of iSS radiological

features (7). Of those, 17 had no features of clinical syndrome (hearing loss,

myelopathy or ataxia). The team focused on describing the radiological features of

iSS and the auditory or vestibular function was not described in the symptomatic

patients, and therefore is the focus of this study.

One of the less common symptoms associated with iSS is loss or reduction of smell

function yet olfaction has not been systemically studied to date. It may be impaired

possibly due to similar pathophysiological processes affecting the olfactory nerve

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(CNI) and CNVIII (8, 64). Therefore, the assessment of olfactory function was included as part of this study.

3.2   Study aims

The aims of this study were to (1) phenotype the audiovestibular function in a radiologically confirmed cohort of patients with iSS, (2) attempt to identify the likely involved segment along the auditory and vestibular pathways by means of the clinical tests, (3) assess the olfactory function in a sample of patients with iSS and (4) determine if an association exists between the olfactory and auditory functions.

3.3   Methods

3.3.1   Study design and setting

This was a cross-sectional study describing audiological, vestibular and olfactory findings of patients with radiologically confirmed iSS and who have been under the care of the Queen Square Superficial Siderosis multidisciplinary team.

3.3.2   Patient inclusion and data collection

Clinical and demographics data were collected, as part of this study, of patients with the known diagnosis of iSS confirmed radiologically according to the radiological diagnostic criteria and who have been under the care of the Superficial Siderosis multidisciplinary team at the National Hospital for Neurology and Neurosurgery, Queen Square, London. Results of the unilateral auditory assessments due to previous surgery, including cochlear implantation, were not included in the study analysis. Olfactory assessment was performed as part of the clinical research project.

3.3.3 Patient characteristics and audiovestibular findings

Patients' characteristics included age, gender, whether a likely causative event for the development of iSS was known and in which case disease duration was calculated in years (from the year of the presumed causative event to the year when the audiovestibular assessment was performed, where likely causative event was not known, disease duration was calculated from the year of diagnosis to the test date). Treatment status (at the time of testing) was ascertained.

Audiological and vestibular/balance test result interpretation and comparisons to normative data were performed as described in Chapter 2 (Methodology). Hearing thresholds were represented by 3- and 4-frequency averages (3FA: 0.5/1/2 kHz; 4FA: 0.5/1/2/4 kHz) calculated from PTA. To calculate 3FA/4FA for patients in whom thresholds were not reached at certain frequencies, the values were substituted by 120 dB HL. Other audiological assessments included tympanometry, OAEs, ART, ABR, speech audiometry and central auditory (processing) tests such as LiSN-S and QuickSiN. The vestibular assessments included optokinetic and rotatory chair tests, vHIT, caloric testing, o/cVEMPs. The audiological and vestibular assessment findings were tabulated in the respective tables. Each case and each side (ear) were evaluated separately, and the results from each test were collated to determine the likely affected segment while taking into consideration the presence of risk factors for secondary auditory or vestibular dysfunctions, as described in Chapter 2 (Methodology).

3.3.4 Olfactory function findings

The olfactory function was assessed using the University of Pennsylvania Smell Identification Tests (UPSIT), a 40-item forced choice test which can be self-administered, by scratching microencapsulated strips of paper to release the odour. Detailed description of UPSIT is provided in Chapter 2 (Methodology). The scores were compared to the normative data provided by the manufacturer, and according to which the categories of olfactory function were derived.

3.3.5 Statistical analysis

Statistical analysis performed as part of this study was described in Chapter 2 (Methodology). In view of some data failing the assumption of normal distribution, non-parametric tests were used to assess for difference between the 3FA/4FA thresholds (both ears) and treatment status (Mann-Whitney U test), and to assess for asymmetry between the 3FA/4FA thresholds for right and left ears (Wilcoxon signed rank test). Correlation analysis was performed to determine if association exists between the 3FA/4FA thresholds and age and disease duration.

In view of the small sample size (n ≤ 50), non-parametric Kendall's Tau-b rank correlation coefficient was used to determine if association exists between the hearing thresholds and age or disease duration (299, 300). Linear regression was performed between UPSIT scores and the hearing thresholds to determine if the association exists and measure the proportion of variance between the hearing thresholds (independent variable) and UPSIT scores (dependent variable).

3.4 Results

3.4.1 Patients' demographics and characteristics

Of 76 patients with the diagnosis of classical iSS, 41 underwent auditory assessment. Of those, data on 35 patients were included in this study and excluded in 6 cases due to records not retrieved in 1 case and in 5 cases due to unilateral results from previous unilateral ear surgery, including cochlear implantation. One or more follow-up (interval) assessment of hearing thresholds (PTA) was performed for 18 patients (n=33) and the date are included in the hearing thresholds analysis.

Of 35 patients, the results of vestibular assessments were available in 26 cases. The audiovestibular assessments took place on the same day in the majority of cases. In 6 cases the auditory and vestibular assessments were performed within 8 months of each other, and in 3 cases they were performed within 17, 24 and 34 months of each other.

Of 35 patients who underwent the auditory assessment, 23 (66%) were male. The median (IQR) age was 56 (32) years at the time of the auditory assessments. The likely causative event was unknown in 3 cases. The median time interval from presumed causative event to the test date (disease duration) was 19 (14) years **(Table 3.1).**

3.4.2 Auditory findings

3.4.2.1 Hearing thresholds

The degree of hearing loss was calculated for right, left and both ears, using 3FA and 4FA, and are presented in **Table 3.1.** In 8 cases, only PTA (and tympanometry)

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results were available without additional hearing tests. In 2 cases, only descriptive

hearing thresholds obtained from clinical summaries were available.

Parameters (years)	Mean	Median	IQR	SD	95% CI	
Age	50.3	55.5	31.8	17.4	46.0-54.5	
Disease duration (n=32)	20.6	19.0	14.0	10.1	18.0-23.3	
Hearing thresholds (n=67)*						≥90th percentile
Right ear 3FA*	51.8	46.7	55.0	36.3	42.9-60.6	46%
Right ear 4FA	55.4	51.3	48.8	35.2	46.8-64.0	52%
Left ear 3FA*	48.0	43.3	60.0	34.3	39.6-56.4	37%
Left ear 4FA	51.7	47.5	53.8	33.8	43.5-59.9	45%
Both ears 3FA*	49.9	43.3	50.8	32.3	42.0-57.8	45%
Both ears 4FA	53.5	49.4	49.4	31.7	45.8-61.2	49%

Table 3.1. Study cohort characteristics: age, disease duration in years, hearing parameters represented by the 3-frequency average (3FA) and 4-frequency average (4FA) audiometric thresholds for each and both ears. Legend: *data failed assumption of normal distribution (Shapiro-Wilk test of normality, p<0.05;).

The degree of hearing loss (right, left, both ears 3FA and 4FA) was compared to the normative data derived from an English population sample (206), the hearing thresholds were at the 90th or worse percentiles in ≥45% cases, except for 3FA left ear thresholds (37%) **(Table 3.1)**.

There was no statistically significant difference in mean ranks between right and left ear thresholds for 3FA (z=-0.99; p=0.320) or for 4FA (z=-1.15; p=0.250).There was also no statistically significant correlation between hearing thresholds (both ears) and age at test (3FA: T_b= -0.050, p=0.551; 4FA: T_b= -0.053, p=0.533) or disease duration (3FA: T_b= -0.160, p=0.082; 4FA: T_b= -0.141, p=0.128). The thresholds for both ears were statistically significantly worse (indicated by higher threshold values) in those receiving treatment (3FA mean rank = 44.2; 4FA mean rank=43.9) than those without treatment (3FA mean rank: 30.2; 4FA mean rank=30.3), 3FA: z=2.38; p=0.017; 4FA: z=2.31; p=0.021).

3.4.2.2 Acoustic reflexes

Acoustic reflex thresholds (ART) were recorded in 10 cases **(Table 3.2)**. ART was recorded with only ipsilateral stimulus in one case and in two cases assessing only one ear. Of the cases which could be reliably interpreted, the pattern of responses was consistent with vestibulocochlear nerve and brainstem (CNVIII/BS) involvement in 4/10 (40%) and in 2/10 (20%) cases with vestibulocochlear nerve (CNVIII) involvement only.

3.4.2.3 Auditory Brainstem Responses

Auditory brainstem responses (ABR) were recorded in 21 patients. ABR was normal in 4/21 (19%) cases. The findings were inconclusive due to bilaterally elevated hearing thresholds in 5 cases and unilaterally elevated in 4 cases. In combination with the presence of other risk factors for hearing loss, results were deemed inconclusive bilaterally in 8/21 (38%) cases. The findings were abnormal in the remaining cases (9/21, 43%) of which 3 were unilateral.

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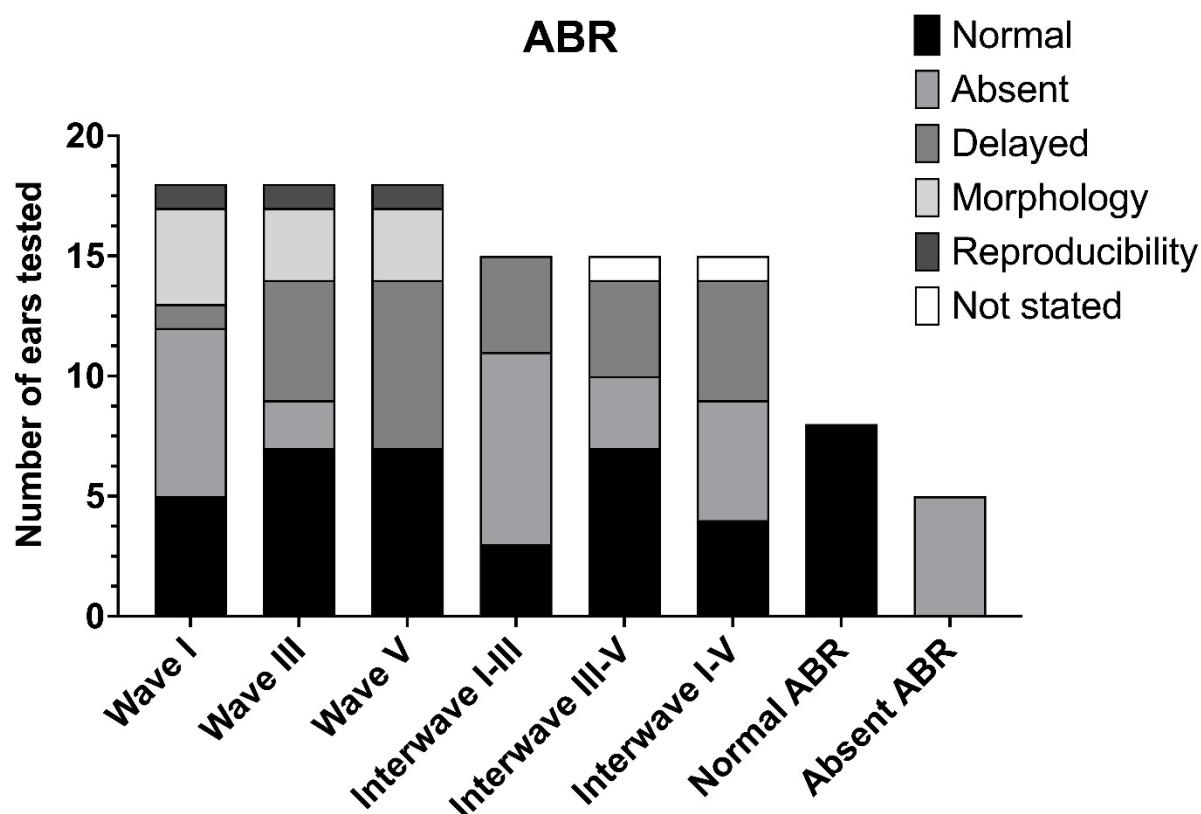
Figure 3.1. Auditory brainstem responses (ABR) findings, excluding the inconclusive cases due to elevated hearing thresholds (n=14 ears).

The most common findings were absent Wave I and delayed Wave V (47% ears each) which impacted calculation of interwave I-III and I-V latencies **(Figure 3.1).**

3.4.2.4 Central auditory tests

LiSN-S was performed in 5 cases and was normal (within 2 SD of the matched normative data) in 1 (20%) case. The most frequently affected measures were "Spatial Advantage" and "High Cue" **(Figure 3.2)** similarly to the pattern observed in spatial processing disorder (231, 309). The QuickSiN performed in 8 cases and in 6 (75%) cases the SNR loss was outside of the normal values.
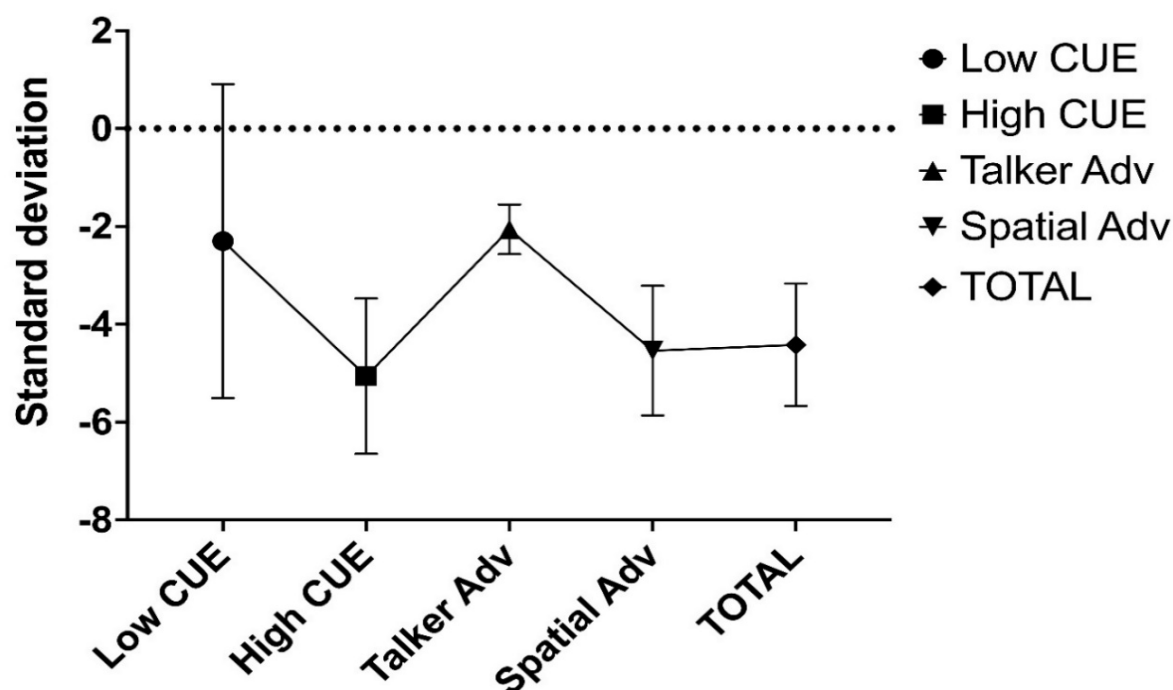
Figure 3.2. Listening in Spatialised Noise- Sentences test (LiSN-S) results. These were available in 5 cases, (mean, SD), which appear worst in High CUE and Spatial Advantage (Adv) domains, and overall. Normal range -2 to 2 SD of the normative data, age- and gender-matched.

3.4.2.5 Likely affected segment of the auditory pathway

The audiological findings were collated to include results of all the tests **(Table 3.2)**. Findings were deemed inconclusive in 12/30 (40%) cases due to likely age-related changes or presence of HL risk factors or in view of elevated thresholds.

Of the patients in whom the results could be interpreted without the confounding factors for hearing loss, retrocochlear involvement was observed in 11/30 (37%) cases, and in two of those (Cases 10 and 21), with no additional risk factors for hearing loss, the hearing thresholds were either normal or mildly elevated. The hearing function was deemed normal in 3/30 (10%) cases, and further 3/30 (10%) cases demonstrated normal retrocochlear auditory function. In 1/30 (3%) further

case, there was unilateral cochlear hearing loss without any associated risk factors for hearing loss or likely age-related changes, however retrocochlear status was not known.

3.4.3 Vestibular findings

Of the 26 patients who underwent vestibular testing, 12 had associated risk factors for central or peripheral vestibular dysfunction.

3.4.3.1 Gaze assessment, oculomotor and rotatory chair tests

Gaze, oculomotor and rotatory chair testing was performed in 25 cases, of which in 2 cases findings from clinical (bedside) assessments were available. The results are presented in **Table 3.3.** The results were normal in 5/25 cases (20%).

3.4.3.2 Video head impulse, bithermal caloric and vestibular-evoked myogenic potentials tests

Video head impulse test results were available in 12 cases. The findings are presented in **Table 3.4.**

Ocular vestibular evoked myogenic potentials tests were performed in 10 cases **(Table 3.4)**. Responses were absent unilaterally in 5/10 (50%) cases, bilaterally in 1/10 (10%) case (deemed due to age) and present bilaterally in 4/10 (40%) cases.

cVEMPs were recorded in 14 cases. Responses were absent: bilaterally in 6/14 (43%) cases – in 3/14 (21%) cases likely due to age, and unilaterally in 1/14 (7%) case. Unilaterally abnormal wave latencies were reported in 1/14 (7%) case. The responses were present bilaterally in 6/14 (43%) cases.

Case	Ear	RF HL	4FA PTA	SiQ	Rollover Y/N	Tymp	OAE	ART	ABR	Quick-SiN	LiSN-S	Likely affected segment
1	Rt	C, R	105			n			INC‡			INC‡
	Lt	C, R	96.3			n			INC‡			INC‡
2	Rt	R	25.5			n	Present		Abn‡			Retro‡
	Lt	C, R	48.8			n	Absent‡		Abn‡			Retro‡, cochlear‡
3	Rt		62.5			Neg		CNVIII/BS‡	INC‡			Retro‡, cochlear INC‡
	Lt		68.8			n		CNVIII/BS	INC‡			Retro, cochlear INC‡
4	Rt	C, R	83.8			n	Absent‡					INC‡
	Lt	C, R	77.5			n	Absent‡					INC‡
5	Rt	C, R	105			n	Absent‡	INC‡	INC‡			Cochlear‡, retro INC‡
	Lt	C, R	120			n	Absent‡	INC‡	INC‡			Cochlear‡, retro INC‡
6	Rt		48.8			n			Abn			Retro, cochlear INC‡
	Lt		56.3			n			INC‡			INC‡, cochlear INC‡
7	Rt		23.8			n						INC‡
	Lt		32.5			Flat						INC‡
8	Rt	C	56.3			n	Absent‡	CNVIII/BS	INC‡	Abn	Abn	Retro, cochlear‡
	Lt	C	42.5			n	Absent‡	CNVIII/BS	Abn	Abn		Retro, cochlear‡

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9	Rt	C, R	Mod	50%	Y	n	Absent‡	Cochlear*‡	Abn‡			Cochlear‡, retro‡
	Lt	C, R	Sev	10%		n	Absent‡	INC‡	INC‡			Cochlear‡, retro INC‡
10	Rt		12.5			n	Present	CNVIII	Abn	Abn	n	Retro
	Lt		10			n	Present	n	Abn	Abn		Retro
12	Rt	C, R	56.6	40%		n	Absent‡		INC‡	Abn‡	Abn‡	Retro‡, cochlear‡
	Lt	C, R	23.8	50%		n	Present		Abn‡	Abn‡		Retro‡
13	Rt		10	88%		n						Normal
	Lt		6.3	81%		n						Normal
14	Rt		35	40%	N	n	Absent‡	INC*				Retro, cochlear‡
	Lt	C	61.3	15%	Y	n	Absent‡	INC*				Retro, cochlear‡
15	Rt		26.3			n	Absent‡	CNVIII	Abn	Abn	Abn	Retro, cochlear‡
	Lt	C	10			n	Absent‡	CNVIII	Abn	Abn		Retro, cochlear‡
16	Rt		120			n			INC‡			INC‡
	Lt		90			n			INC‡			INC‡
18	Rt		50			n		CNVIII/BS	Abn			Retro, cochlear INC‡
	Lt		68.8			n		CNVIII/BS	Abn‡			Retro, cochlear INC‡
20	Rt		12.5		N	n	Present		n			Normal
	Lt		15			n	Present		n			Normal
21	Rt		16.3			n	Present		Abn		Abn	Retro,
	Lt		23.8			n	Present		Abn			Retro,

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22	Rt	C, R	120								INC‡
	Lt	C, R	120								INC‡
23	Rt	C, R	87.5			n		INC‡	INC‡			INC‡
	Lt	C, R	65			n		INC‡	INC‡			INC‡
24	Rt	C, R	36.3		N	n						Cochlear‡,
	Lt	C, R	97.5		Y	n						Cochlear‡, retro‡
25	Rt	C, R	20			n	Absent‡		n	Abn		Cochlear‡, retro‡
	Lt	C, R	13.8			n	Absent‡		n	Abn		Cochlear‡, retro‡
26	Rt	C	52.5			n			Abn			Retro, cochlear INC‡
	Lt	C	55			n			Abn			Retro, cochlear INC‡
27	Rt		50	87%	N	n						Cochlear‡,
	Lt		48.8	85%	N	n						Cochlear‡,
28	Rt		13.8			n	Present		n	n		Normal
	Lt		7.5			n	Present		n	n		Normal
29	Rt	C, R	27.5			n						INC‡
	Lt		120			n						INC‡
30	Rt		41.3			n		CNVIII/BS	Abn	Abn		Retro, cochlear INC‡
	Lt		38.8			n		CNVIII/BS	Abn	Abn		Retro, cochlear INC‡
31	Rt		31.3			n			n	n		Cochlear‡,
	Lt		33.8			n			n	n		Cochlear‡,

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32	Rt		16.3			n	Present					Normal cochlear, retro INC‡
	Lt		12.5			n	Absent					Cochlear, retro INC‡
33	Rt	C	33.8			n			Abn			Retro, cochlear INC‡
	Lt	C	45			n			Abn			Retro, cochlear INC‡

Table 3.2. Summary of the cohort's audiological findings and assessment of the likely affected segment. Findings presented cases by case, taking into account age (if ≥60 years or not); presence of risk factors (RF) for hearing loss (HL) indicated as of cochlear (C) or retrocochlear (R) origin or both (C, R); speech audiometry (in quiet), where performed, including if rollover phenomenon present (N, no; Y, yes) or not; tympanometry and middle ear status; otoacoustic emissions (OAEs) whether present (Pres) or absent (Abs); results of acoustic reflex thresholds (ART), auditory brainstem responses (ART) and central auditory (processing) tests. The latter include Quick speech-in-noise (QuickSiN), Listening in Spatialised Noise-Sentences, LiSN-S) tests. Legend: †inconclusive in view of negative tympanogram (immittance); *unilateral ART; ‡ in view of elevated hearing thresholds or risk factors for hearing loss or likely age-related; Abn abnormal; INC inconclusive; Mod moderate; n normal; n/a not available; Retro retrocochlear; Sev severe.

Caloric testing was performed in 10 cases: caloric responses were normal in 3/10 (30%) cases; bilateral and unilateral hypofunction was demonstrated in 3/10 (30%) cases each; and findings suggestive of central vestibular dysfunction were identified in 1/10 (10%) case **(Table 3.4).**

3.4.3.3 Likely affected segment of the vestibular pathway

The evaluation of the results for likely affected segment of the vestibular pathway were performed for each case (and ear) and are presented in **Table 3.5.** Of the 26 cases which were evaluated for vestibular dysfunction, 2/26 (8%) cases had entirely normal vestibular function; 1/26 (4%) further case had normal function was recorded albeit the results not reported for some of the tests; normal unilateral vestibular function was identified in 2/26 (8%) cases.

Central vestibular (that involving proximal vestibular pathway commencing from the Scarpa's ganglion) dysfunction was recorded in 19/26 (73%) cases whether due to the presence of associated secondary risk factors for central involvement or due to iSS, and in 14/26 (54%) of which additional peripheral vestibular dysfunction was identified.

Bilateral peripheral vestibular involvement (in the absence of central findings) was identified in 2/26 (8%) cases.

3.4.4 Olfactory function assessment

Results of olfactory function assessment were available in 10 cases and identified olfactory dysfunction in all: mild microsmia in 4 cases, moderate microsmia and anosmia in 3 cases each. The mean (SD) of UPSIT score was 25.5 (7.8).

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Linear regression analysis identified statistically significant association between UPSIT scores and hearing thresholds for both ears 3FA: R=0.746; 95% CI -0.25 to -0.04; p=0.013); the scores variability was accounted by hearing thresholds in 55.7% (adjusted R^2 =50.2%); for 4FA analysis: R=0.716; b=-0.143; 95% CI -0.257 to -0.029; p=0.02); the scores variability was accounted by hearing thresholds in 51.2% (adjusted R^2 =45.1%) (310). UPSIT scores decreased by 0.145 and 0.143 unit increase in hearing thresholds for 3FA and 4FA, respectively (b=-0.145; b=-0.143) (310).

Case	Gaze	Saccades	SP	OKN	Sinusoidal	VOR suppr	Step rotation	Findings
1	Normal	Abn‡	Abn‡	Normal	Low gain, increased phase	Normal	Normal b/l	Central‡, peripheral
2	Normal	Normal	Normal	Normal	Normal	Normal	Normal b/l	Normal
3	RBN WF/WOF on Rt gaze LBN WOF on Lt gaze	Abn	Abn‡	Normal	Normal	Abn	Low TC b/l	Central, peripheral
4	RBN WOF on Rt gaze	Abn	Abn‡	Normal	Increased phase	Abn	Rt DP	Central‡, peripheral (Lt hypofunction)
5	No cerebellar signs†							Normal†
6	Bi-directional gaze-evoked nystagmus	N/S	Abn	Abn	N/S	Abn	Low TC b/l	Central, peripheral
7	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
8	Normal	Normal	Abn	Abn	Increased gain	Abn	Normal b/l	Central
10	Bi-directional gaze-evoked nystagmus WOF	Abn	Abn	Abn	Normal**	Abn**	Low TC Rt	Central, peripheral (Rt hypofunction)
12	LBN WOF on central/Lt gaze	Normal	Abn‡	Abn	Increased phase	Normal	Low TC b/l	Central, peripheral
14	N/S	Normal	N/S	Normal	Normal	Normal	Normal	Normal (SP, gaze findings not stated)

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15	Normal	Abn‡	Normal	Abn‡	Normal	Normal	Normal b/l	Central‡
18	Normal	Normal	Abn‡	Normal	Normal	Normal	Low TC b/l Rt DP	Central‡, peripheral (Lt hypofunction)
20	Bi-directional gaze-evoked nystagmus‡†	Abn‡	Abn‡	Normal	Normal	Abn	N/S	Central‡†
21	Normal	Abn	Abn	Normal	Normal	Normal	Normal	Central
22	Vertical nystagmus‡	Normal	Normal	Abn‡	Reduced gain^	Normal	Low TC b/l	Central‡ peripheral‡
23	Normal	Abn‡	Abn‡	Abn	Normal	Abn	Low TC b/l	Central‡, peripheral
24	Normal	Normal	Normal	Normal	N/S	N/S	N/S	Normal
25	Ocular flutter‡	Normal	Normal	Normal	Reduced gain^	Normal	Normal b/l	Central‡
26	Vertical nystagmus	Abn	Abn‡	Abn	Increased phase	Abn	Low TC b/l	Central‡, peripheral
27	Normal	Abn	Abn‡	Normal	Normal	Normal	Normal	Central
28	Normal	Normal	Normal	Normal	Reduced phase; normal gain	Normal	Normal	Peripheral‡
29	LBN on Lt gaze WF, downbeat on Rt/Lt gaze WOF; LBN on up-gaze WOF	Normal	Abn‡	Abn	Increased phase	Abn	Normal	Central
30	RBN on Rt gaze WOF	Abn‡	Abn‡	Abn‡	Increased phase, Reduced	Abn‡	Low TC b/l	Central‡, peripheral (Lt>Rt)

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				gain^			
31	Normal	Abn	Normal	Normal	Normal	Abn	Normal b/l	Central

Table 3.3. Table of the findings from gaze, oculomotor and rotatory chair assessments. Legend: Abn abnormal; LBN left beating nystagmus; Lt left; Nyst nystagmus; OKN optokinetic nystagmus; RBN right beating nystagmus; Rt right; SHA sinusoidal harmonic acceleration; SP smooth pursuit; Suppr suppression; VOR vestibulo-ocular reflex; WOF without fixation; WF with fixation; **SHA/VOR suppression at 0.2Hz; ‡due to presence of risk factors for vestibular dysfunction or deemed due to age-related changes; †bedside assessment with peripheral function assessed with other tests: ^inconclusive due to noisy trace.

Case	Side	vHIT						Side	oVEMP	cVEMP	Caloric test*	
		Ant	CS	Lat	CS	Post	CS					
1	Rt							Rt	-	-	100% CP	
	Lt							Lt	n	-	n	
3	Rt							Rt			n	
	Lt							Lt			n	
4	Rt	n/a	n/a	0.89	-	0.47	Y	Rt	n	n		
	Lt	0.68	-	0.68	-	n/a	n/a	Lt	n	n		
5	Rt							Rt		-	Hypof	
	Lt							Lt		-	Hypof	
6	Rt							Rt			n	
	Lt							Lt			n	
7	Rt			0.99	-			Rt				
	Lt			1.0	-			Lt				
8	Rt	0.96	-	0.99	-	0.84	-	Rt	n	n		
	Lt	0.95	-	0.95	-	0.87	-	Lt	n	-		
10	Rt	0.85	-	0.98	-	0.72	Y	Rt	n	n		
	Lt	0.62	-	0.96	-	0.84	Y	Lt	n	n		
12	Rt	0.85	-	0.77	Y	0.44	Y	Rt	-	-‡		
	Lt	0.86	-	0.69	Y	0.91	-	Lt	n	-‡		
13	Rt							Rt			Rt DP	
	Lt							Lt			Hypof	
15	Rt	0.69	-	0.95	Y	0.56	-	Rt	n	n		
	Lt	0.51	Y	0.91	Y	0.75	-	Lt	-	n		
18	Rt							Rt		-**	n	
	Lt							Lt		-**	38% CP	
20	Rt							Rt			n	LOS
	Lt							Lt			n	LOS
21	Rt	0.48	-	0.54	Y	0.35	-	Rt	n	n		
	Lt	0.58	-	0.58	Y	0.45	Y	Lt	-	n		

ID	Ear	A	CS	L	CS	P	CS	Ear	oVEMP	cVEMP	Caloric
22	Rt							Rt		n	Hypof
	Lt							Lt		n	Hypof
23^	Rt	0.60	-	0.56	Y	0.24	Y	Rt	n	-‡	
	Lt	0.24	-	0.17	Y	0.16	Y	Lt	-	-‡	
24	Rt							Rt	n	n	n
	Lt							Lt	n	delay lat	n
26^	Rt	n/a	n/a	1.01	Y	0.33	Y	Rt			
	Lt	0.43	-	0.99	Y	n/a	n/a	Lt			
27	Rt	n/a	n/a	0.97	Y	n/a	n/a	Rt			
	Lt	n/a	n/a	0.86	Y	n/a	n/a	Lt			
29a	Rt	0.54	-	0.93	Y	0.18	-	Rt			
	Lt	0.65	-	0.87	Y	0.45	-	Lt			
30	Rt							Rt	-‡	n	Hypof
	Lt							Lt	-‡	n	Hypof
31	Rt	0.99	-	1.13	-	0.85	Y	Rt		-‡	
	Lt	0.78	-	1.03	-	0.98	-	Lt		-‡	

Table 3.4. Findings from: video head impulse test (vHIT), vestibulo-ocular reflex (VOR) gains are reported for right (Rt) and left (Lt) ears, anterior (A), lateral (L, horizontal) and posterior (P) semicircular canals (SCC) with (Y) or without (-) corrective saccades (CS); vestibular evoked myogenic potentials presented at 105dB SPL (ocular, oVEMP and cervical, cVEMP), presented as 105 decibel sound pressure level (dB SPL); caloric irrigation testing. Legend: - not recorded/absent (corrective saccades or VEMP response); ‡ likely due to age-related changes to vestibular function; *stated as normal or hypofunction (hypof) as reported in clinical letters; **cVEMP was presented at 125 dB SPL; ^insufficient eye tracking during RALP; CP canal paresis; Lat wave-latency; LOS lack of suppression with otherwise normal responses; n normal, n/a not assessed; Y corrective saccades present.

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Case	Side	G/OM/RC Central	G/OM/RC Peripheral	VHIT	Caloric	oVEMP	cVEMP	Likely affected segment
1	Rt	X‡	X		X	X	X	Central‡, peripheral
	Lt	X‡	X		n	n	X	Central‡, peripheral
2	Rt	n	n					Normal
	Lt	n	n					Normal
3	Rt	X	X		n			Central, peripheral
	Lt	X	X		n			Central, peripheral
4	Rt	X‡	n	P SCC		n	n	Central‡, peripheral
	Lt	X‡	X	Central		n	n	Central‡; peripheral
5	Rt	n		L SCC‡	X‡		X‡	Peripheral‡
	Lt	n		L SCC‡	X‡		X‡	Peripheral‡
6	Rt	X	X		n			Central, peripheral
	Lt	X	X		n			Central, peripheral
7	Rt	n	n	n				Normal
	Lt	n	n	n				Normal
8	Rt	X	n	n		n	n	Central
	Lt	X	n	n		n	X	Central, peripheral
10	Rt	X	X	P SCC		n	n	Central, peripheral

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	Lt	X	n	Central		n	n	Central
12	Rt	X	X	Central, P SCC		X	X‡	Central, peripheral
	Lt	X	X	L SCC		n	X‡	Central, peripheral
13	Rt							Normal*
	Lt				X			Peripheral*
14	Rt	n	n					Normal^
	Lt	n	n					Normal^
15	Rt	X‡	n	Central‡		n	n	Central‡
	Lt	X‡	n	Central‡, A SCC		X	n	Central‡, peripheral
18	Rt	X‡	X	n/a	n		X	Central‡, peripheral
	Lt	X‡	X	n/a	X		X	Central‡, peripheral
20	Rt	X‡	n		n			Central‡^^
	Lt	X‡	n		n			Central‡^^
21	Rt	X	n	Central, L SCC	n/a	n	n	Central, peripheral
	Lt	X	n	Central, L/P SCC	n/a	X	n	Central, peripheral
22	Rt	X‡	X‡		X‡		n	Central‡, peripheral‡
	Lt	X‡	X‡		X‡		n	Central‡, peripheral‡
23	Rt	X‡	X	Central, L/P SCC		n	X‡	Central‡, peripheral
	Lt	X‡	X	Central, L/P SCC		X	X‡	Central‡, peripheral

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24	Rt	n			n	n	n		Normal^^^
	Lt	n			n	n	X		Peripheral^^^
25	Rt	X‡	n						Central‡
	Lt	X‡	n						Central‡
26	Rt	X‡	X	Central, P SCC					Central‡, peripheral
	Lt	X‡	X	Central					Central‡, peripheral
27	Rt	X	n	Central					Central
	Lt	X	n	Central					Central
28	Rt	n	X						Peripheral‡
	Lt	n	X						Peripheral‡
29	Rt	X	n	Central					Central
	Lt	X	n	Central					Central
30	Rt	X‡	X	n/a	X	X‡	n		Central‡, peripheral
	Lt	X‡	X	n/a	X	X‡	n		Central‡, peripheral
31	Rt	X	n	Central			X‡		Central
	Lt	X	n	Central			X‡		Central

Table 3.5**.** Summary of the overall vestibular findings and assessment of the likely segment affected, including gaze, oculomotor and rotation chair (G/OM/RC) tests (from **Table 3.3**); video head impulse test (vHIT) assessing anterior (A), lateral (horizontal, L) or posterior (P) semicircular canals (SCC) (from **Table 3.4**);caloric irrigation testing, assessing lateral (horizontal) SCC; vestibular

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evoked myogenic potentials (ocular, oVEMP assessing utricular/superior vestibular nerve (U/SVN) function; cervical, cVEMP, assessing saccular/inferior vestibular nerve (S/IVN) function). Legend: Lt left; n normal; n/a not assessed; Rt right, X abnormal; ‡vestibular dysfunction likely due to age-related changes (age ≥60), or in view of secondary risk factors for vestibular hypofunction; *assuming no central findings on caloric testing; ^smooth pursuit or gaze test results not stated; ^^impulse rotatory test results not stated; ^^^results from sinusoidal harmonic acceleration, VOR reflex and impulse rotatory tests not stated.

3.5 Discussion

The AViSS study describes auditory and vestibular findings from a large cohort of individuals diagnosed with iSS. In the majority of cases, the audiovestibular assessments included at least two auditory and vestibular tests and allowed to determine end-organ involvement versus more proximal origin of the audiovestibular dysfunction. Presence of risk factors (and the likely involved segment of the audiovestibular pathway) was accounted for when interpreting the results which was necessary to reliably determine the likely site of lesion within the audiovestibular pathway.

The results of the AViSS study support the current evidence of predominantly retrocochlear origin of hearing loss in iSS. This was identified in all cases except one ear (2%) in which it was deemed of cochlear origin and in the absence of associated risk factors or age-related changes. Normal hearing function (confirmed on PTA and at least one other auditory test) was present in three patients in whom disease duration was calculated between 19 and 34 years. It is plausible that retrocochlear hearing loss may precede cochlear involvement possibly with an antegrade pattern of involvement of the auditory pathway. However further dedicated longitudinal studies are needed to monitor hearing for progression of hearing loss over time, identify likely involved segment of involvement at baseline and over time.

Due to a large number of the individuals with other risk factors for hearing loss (than iSS) or likely age-related changes, it was difficult to ascertain whether the cochlear or retrocochlear involvement was reflected in the auditory thresholds.

The results of ART demonstrated the pattern suggestive of brainstem and cochlear nerve involvement in the majority of tested ears – these findings were corroborated by the ABR results (absent or abnormal responses in the majority of cases). Absent or abnormal responses of Wave I was the most common abnormality of ABR test results, which inadvertently impacted interwave I-III and I-V latencies findings.

Wave I abnormalities may be suggestive of the involvement of distal segment of the cochlear nerve while delayed latencies of Wave I-V and may be due to the demyelinating processes affecting the cochlear nerve from lipid peroxidation from the free iron species in iSS. Findings of prolonged neural conduction of Waves I–III and I–V interpeak latencies were identified in a cohort of patients with demyelinating type Charcot-Marie-Tooth (Type 1A, CMT1A) (311).

This is the first study to also report central auditory findings in iSS cohort and it follows from the findings in the previous case report which were included in this study (43).The central auditory testing with LiSN-S has identified the pattern similar to that characteristic of spatial processing disorder (SPD) and brainstem involvement, with the lowest scores observed in high cue and spatial advantage domains. Similar pattern was observed in a study involving individuals with Friedreich's ataxia (FRDA) and CMT (309, 311). Both these groups of patents have been shown to have impaired spatial perception from inability to integrate binaural cues which can impact the perception of speech in the presence of background noise (311).

This study's findings confirm that iSS-related hearing loss is likely to be worse than appropriate for age, and clinicians should have a low threshold for suspecting iSS in

patients presenting with hearing loss which is more marked than age-matched norms or tests suggest retrocochlear involvement or both, and particularly if history of previous CNS trauma or surgery or if symptoms of imbalance, memory problems, olfactory dysfunction are present.

The study demonstrates hearing thresholds were worse for those patients who were receiving treatment as the mean ranks for hearing levels for individuals during treatment (either medical chelation therapy or following surgical repair) appeared worse than for those who were not on treatment. This is possibly due to the initiation of treatment due to disease progression which might have manifested as deterioration in hearing. Improvements in hearing while during treatment had been previously reported, but were based on patients' subjective reports, and were observed at low frequencies in one ear in one of our patients likely due to vibration from the PTA test stimulus (75). Further studies are needed to assess auditory function during the treatment trials by means of PTA and possibly electrophysiological measure such as ABR.

The vestibular findings identified central vestibular involvement in the majority of cases, likely in keeping with the radiological diagnosis of iSS, in which haemosiderin may be observed over the cerebellar vermis and folia.

The findings of normal hearing in 3 cases and normal vestibular function in 2 cases suggest that MRI findings diagnostic of iSS may, if detected early, precede the onset of audiovestibular impairment. Widespread availability of MRI and particularly paramagnetic sequences which are known to be more sensitive in identifying hemosiderin deposits, individuals with iSS may be diagnosed at an earlier stage than

had been in the past, and early initiation of treatment may be facilitated which would help with halting or slowing disease progression.

This study attempted to identify the likely site of lesion for hearing loss in the iSS patients and to showcase the approach for evaluating auditory and vestibular functions in individuals with complex neuro-otological conditions.

3.5.1 Study limitations

There are several limitations to our study, the main of which is its retrospective nature. While the sample size of the cohort should be considered large (in comparison to other studies of similar nature), several test modalities were performed in a small number of cases. During analysis of the site of lesion assessment it was clear that a large number of patients within the cohort had presence of other risk factors which may impair auditory or vestibular function (or both) and thus this impacted the interpretation of the audiovestibular results for site of lesion identification. It was not possible to retrieve full information on post cochlear implantation outcomes, and therefore this was not reported.

AViSS is a cross-sectional and in part retrospective observational study. The limitations arising from its design include its retrospective nature which has limited the availability of test results and clinical records in several cases, and in some cases the clinical records could not be retrieved. Similar to other studies which describe audiovestibular findings in individuals with iSS, the AViSS study reports the findings from the assessments which varied between cases, and most patients and study participants did not undergo the uniform test battery. This was due to several

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factors, such as the presence of contra-indications to performing specific tests, or due to other patients' factors such as high hearing thresholds, in which cases limited auditory test battery was performed. Similarly, the vestibular assessments needed to be tailored to the patients' factors such as age, and the presence of contra-indications, particularly for caloric or vHIT tests. The testing regimen was also tailored to minimise the participants' time in the department – as part of COVID-19 precautions. Furthermore, as mentioned earlier, the prospective study recruitment and participants' numbers were minimal – in view of COVID-19 pandemic.

Conclusion

This study identifies predominantly retrocochlear hearing loss including central auditory findings in some individuals. This suggests mixed involvement along the auditory pathway at the level of cochlear nerve, brainstem and beyond. The findings also indicate that the thresholds are elevated in almost half of the study individuals, when compared to the thresholds derived from the age- and gender-matched normal population. The findings of the vestibular dysfunction indicate predominantly central (cerebellar or other proximal central vestibular structures') involvement with or without peripheral vestibular involvement – in cases in which peripheral vestibular loss cannot be attributed to the cause of iSS. And lastly, the prevalence of olfactory dysfunction in iSS appears to be high, as identified in this study, and it may correlate with the auditory dysfunction, however due to very small sample size these findings should be interpreted with caution.

CHAPTER 4   QUASARS STUDY

RADIOLOGICAL EVALUATION OF HAEMOSIDERIN USING THE QUEEN

SQUARE SUPERFICIAL SIDEROSIS ANATOMICAL RATING SCALE

4.1   Introduction

Currently, MRI is the reference standard for diagnosing iSS as it allows to

demonstrate haemosiderin in vivo (65). The characteristic pattern of involvement of

infratentorial regions including the cerebellum, brainstem and cranio-cervical junction

forms the basis of the iSS radiological diagnostic criteria (7, 69). This study looks at

the imaging rating scale – titled QUeen squAre (infratentorial) superficial Siderosis

Anatomical Rating Scale (QUASARS) – which was developed with the collaboration

of the Superficial Siderosis multidisciplinary team as a means to assess and quantify

the radiological burden of haemosiderin in infratentorial superficial siderosis. The

study aims were to: 1) determine its reliability; 2) radiologically quantify the extent of

haemosiderin deposits based on anatomical distribution, 3) determine if the imaging

findings correlate with the audiovestibular function of patients with iSS.

4.2   Methods

The full methodology pertaining to this chapter, including the description of the rating

scale, is provided in detail in Chapter 2.

4.2.1   Study design and setting, data collection and imaging protocols

This was a cohort study describing clinical imaging findings using a newly developed

imaging rating scale from a cohort of patients with a known radiological diagnosis of

iSS.

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Each scan (T2-weighted or paramagnetic-sensitive sequences, whether SWI or T2*GRE sequences, or both) was reviewed to identify signal changes suggestive of haemosiderin deposits in anatomical distribution. Scores were collected for each such anatomical region and calculated (summated) to obtain a total score for each scan (pairs of: T2-weighted and a paramagnetic-sensitive sequences) using the QUASARS scale.

MR imaging of the brain was reviewed which followed this (inclusion) criteria:

- Of the patients who had been diagnosed with iSS and under the care of the Superficial Siderosis multidisciplinary team (between June 2004 and December 2021) and who underwent auditory or vestibular testing or both;
- included the sequences: T2-weighted or paramagnetic-sensitive (T2*GRE, SWI) or both;
- which would allow the visualisation of all QUASARS regions and free of any significant imaging artefacts;
- performed within the shortest time interval from the audiological or vestibular tests.

The imaging was not reviewed as part of this study in the following cases (exclusion criteria):

- Imaging of other modalities than MRI;
- MR Imaging of the body regions other than the brain; for example spinal MRI;
- MRI of the patients diagnosed with other types of superficial siderosis than classical iSS, for example cSS;

- MRI of the head that did not allow visualisation of all the anatomical regions
  included in QUASARS, such as an MRI artefact from a cochlear implant;

- MRI of the patients who did not undergo auditory or vestibular (or both) testing or
  whose test results were not available or not retrievable.

Data collection included:

- Patients' characteristics;

- Findings from auditory assessment including PTA averages for 3-frequency
  (3FA) and 4-frequency (4FA) for right, left and both ears; the findings described in
  detail Chapter 3;

- Vestibular assessment results: the findings described in detail in Chapter 3;

- QUASARS scores from the 30 scan-pairs to calculate inter-rater agreement; from
  the 10 scan-pairs to calculate intra-rater agreement.

More information about the data collection, imaging protocols, including the level of
training received, are described in detail in Chapter 2.

4.2.2   <u>Assessment of instrument's reliability</u>

To calculate the inter-rater agreement, thirty pairs of T2-weighted and the
paramagnetic-sensitive images were rated independently by the two raters (Rater 1:
clinical senior neuroradiology fellow in the final year of the higher specialist training
with the Royal College of Radiologists; Rater 2: researcher), blinded to each other's
scores and to the patients' clinical details. To calculate the intra-rater agreement; ten
scan-pairs (T2-weighted and paramagnetic sequences (SWI/T2*GRE) for each scan)
were reviewed by each rater, blinded to own scores.

4.2.3 Assessment of audiovestibular function

The audiovestibular function was assessed – as part of the AViSS study described in Chapter 3; the description its methodology is included in Chapter 2.

Auditory assessments were available for 35, of which PTA was available to record 3FA/4FA in 33 cases patients. The median (IQR) time interval between the MRI and auditory assessment was 1 (8) months; in 6 cases, it was greater than 12 months, ranging between 14 and 23 months.

Vestibular assessments, available from 23 patients, were performed (median, IQR) within 3 (14) months of the MRI. In 8 cases, the time interval between the vestibular assessments and MRI was greater than 12 months, ranging between 15 and 23 months.

4.2.4 Statistical analysis

Comparison of the scores from the entire cohort was performed to assess for asymmetry between right and left sides and correlation analyses between the scores and age, disease duration and hearing thresholds.

Details of the statistical analyses are included in Chapter 2 (Methodology). Additional description of the statistical analysis pertaining to this study is included below.

Intraclass correlation coefficient (ICC) was calculated using two-way mixed effect model to evaluate inter- and intra-rater reliability for absolute agreement. The levels of agreement were interpreted as follows: excellent > 0.90; 0.75-0.90 as good; 0.50-0.74 as moderate and < 0.50 as poor (312).

Non-parametric Kendall's Tau-b rank correlation was used to determine the correlation between the QUASARS scores and the participants' age or disease-duration (calculated as time-interval in years from presumed causative event to the scan) or hearing thresholds (3FA, 4FA).

4.3 Results

4.3.1 Patients' characteristics

The results from 35 patient scans which were reviewed. In 4 cases additional (interval) imaging with interval PTA were available and included in the analysis. In 4 other cases, only T2-weighted images were available for review (without the corresponding paramagnetic-sensitive sequences) and are included in the study.

The median (IQR) age at scan was 57 (20) years. Disease duration was calculated in 34 cases, with mean (SD) of 22 (11) years. The patients' characteristics including the hearing thresholds are reported in **Table 4.1.**

Parameters (n=35)	mean	median	SD	95%CI	IQR	
Age at time of scan (years)*	55.5	57.0	14.0	50.9-60.0	20.0	
Disease duration (years)	21.8	21.5	11.3	17.9-25.8		15.5
Hearing thresholds (n=33)	mean	median	SD	95%CI	IQR	min-max
Both ears 3FA*	45.6	42.5	31.0	35.2-55.9	42.1	3.3-120
Both ears 4FA*	50.0	46.9	31.2	39.6-60.4	45.3	8.1-120

Table 4.1. Study cohort characteristics including hearing thresholds. Hearing thresholds are represented by 3- (3FA) and 4-frequency averages (4FA). Legend: CI confidence intervals; IQR interquartile range; SD standard deviation.

4.3.2 Instrument reliability assessment

Thirty MRI scans were reviewed by both raters to calculate the inter-rater agreement. There was no statistically significant difference in scores between the Rater 1 (clinical specialist neuroradiology senior fellow) and Rater 2 (researcher) for either T2-weighted or paramagnetic-sensitive (SWI/T2*GRE) sequences. The calculated ICC reliability results are presented in **Table 4.2**, demonstrating excellent levels of inter- and intra-rater agreement (ICC >0.9, p<0.001).

Inter-rater reliability (n=30 scan pairs)						
	T2-weighted scores			**SWI/T2*GRE scores**		
	ICC	**95% CI**	**p-value**	**ICC**	**95% CI**	**p-value**
	0.965	0.928, 0.983	**<0.001****	0.961	0.918, 0.981	**<0.001****
Intra-rater reliability (n=10 scan pairs)						
Rater 1	0.960	0.716, 0.991	**<0.001****	0.994	0.979, 0.999	**<0.001****
Rater 2	0.965	0.862, 0.991	**<0.001****	0.968	0.869, 0.992	**<0.001****

Table 4.2. Reliability analysis for scan-pairs for T2-weighted and paramagnetic-sensitive sequences. The latter included Susceptibility Weighted Imaging, SWI or T2* Gradient Recalled Echo, T2*GRE. Two-way mixed effect model was used to calculate intraclass correlation coefficient (ICC) to determine inter-and intra-rater (absolute) agreement; the level of significance was set at 0.05; asymptotic 2-tailed p-values and 95% confidence intervals (CI) provided; **significant at 0.01 level.

4.3.3 Overall findings

The frequency of involvement of each anatomical region of QUASARS for the entire cohort is provided in **Figure 4.1**. The most frequently involved regions observed both on T2-weighted and paramagnetic-sensitive (SWI/T2*GRE) sequences were

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superior vermis (100%) and cerebellar folia (99% of T2-weighted and 100% of SWI/T2*GRE sequences), followed by dorsal midbrain, pons, medulla and ventral midbrain; as expected in line with the iSS radiological diagnostic criteria (7). Involvement of Sylvian fissures was as almost as common as of CNVIII on paramagnetic-sensitive (SWI/T2*GRE) sequences (73% and 74%, respectively); and was equally as common on T2-weighted imaging (49% for Sylvian fissure and CNVIII).

The median (IQR) scores for T2-weighted and paramagnetic-sensitive (SWI/T2*GRE) images were: 17 (16) and 29 (12), respectively **(Table 4.3)**. The scores for paramagnetic-sensitive (SWI/T2*GRE) images were higher than the T2-weighted scores (U=276.0; z=-3.301; p=0.001). There was no statistically significant correlation between the QUASARS scores and disease duration **(Table 4.3)**.

4.3.4 Asymmetry assessment

To confirm symmetrical distribution of haemosiderin deposits between the right and left sides, which is a necessary radiological diagnostic criterion (7), the related-samples Wilcoxon signed ranks test was performed. There was no difference identified in the overall scores between the right and left side for either sequence (T2-weighted: U= 217.0; z=1.107; p=0.268; SWI/T2*GRE: U=140.5; z=1.89; p=0.059), nor in the scores for the infratentorial region only, for either sequence (T2-weighted: U= 44.0; z=1.07; p=0.285; SWI/T2*GRE: U= 24.0; z=1.89; p=0.059).

4.3.5 Correlation of QUASARS scores and audiometry (PTA)

Pure-tone audiometry

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Correlation analysis was performed between the rating scale scores and the

patients' characteristics. A statistically significant moderate correlation was identified

between the overall QUASARS scores and (3FA/4FA) hearing thresholds for both

ears, for both sequences (T2-weighted and SWI/T2*GRE), Kendall's tau-b (Tb) 0.27-

0.29; p<0.05; but not for disease duration **(Table 4.3)**.

Statistically significant (predominantly) strong correlations were present between the

hearing thresholds and: ipsilateral CNVIII; ipsilateral CNVIII and Sylvian fissure, and

contralateral CNVIII and Sylvian fissures haemosiderin appearances on

paramagnetic-sensitive sequences (Kendall's tau-b (Tb) 0.29-0.40; p<0.05) **(Table

4.3)**.

4.3.6   QUASARS scores and auditory and vestibular findings (Chapter 3)

The auditory and vestibular findings (from Chapter 3) are presented with

corresponding QUASARS scores in **Table 4.4**. The lowest QUASARS scores (4 - 8)

were observed in 3 cases, with scores (Cases 7, 9 and 25) and demonstrated

normal and mildly elevated thresholds levels likely due to conductive hearing loss

and possibly secondary to age-related changes (Case 7); and normal vestibular

function. In Cases 9 and 25, the auditory findings were deemed to be of

cochlear/retrocochlear origin, likely due to the risk factors other than iSS. In Case 25,

the vestibular assessment identified presence of ocular flutter suggestive of central

vestibular impairment, however there were no significant findings on the remainder

of VNG oculomotor or rotation chair testing (reduced gain on the sinusoidal harmonic

acceleration test was deemed inconclusive due to presence of ocular flutter as it may

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have affected the results from sinusoidal harmonic acceleration test). Vestibular function was not assessed in Case 9.

In further 3 cases (Cases 13, 20, 32) of the 4 cases in which only T2-weighted imaging was available and rated, low QUASARS scores (range 4-5) were demonstrated, and in all three cases the hearing thresholds were within normal range, according to the BSA criteria (203). The vestibular findings for the corresponding cases identified likely normal peripheral vestibular function in the right ear and hypofunction in the left ear (Case 13), central function due to presence of other factors than iSS (Case 20). In case 32, the vestibular function was not assessed.

Normal vestibular function was identified in Case 2 and 24 however their corresponding QUASARS scores (for SWI) were 32 and 30 suggesting that the radiological findings might precede the onset of vestibular dysfunction in some individuals with iSS.
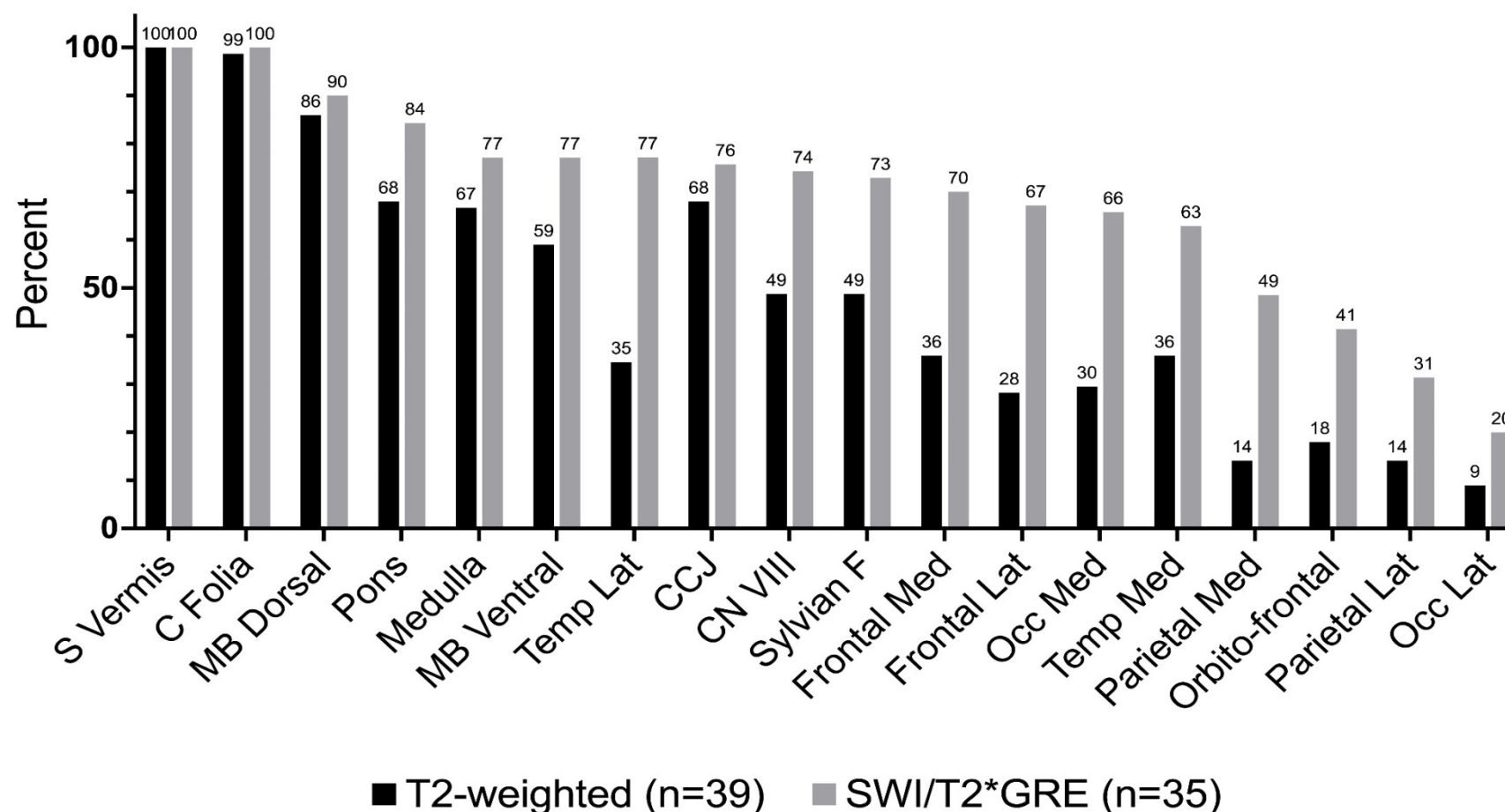
Figure 4.1. Percent involvement of anatomical regions observed on T2-weighted and paramagnetic-sensitive sequences. The latter included susceptibility-weighted imaging, SWI or T2* gradient echo, T2*GRE sequences. Legend: CCJ craniocervical junction; C Folia cerebellar folia; CN VIII 8th cranial nerve; F Fissure; Lat lateral; MB midbrain; Med medial; Occ occipital; S Vermis superior vermis; Temp temporal.

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A. Rating scale scores (overall)	mean	median	SD	95% CI	IQR	min-max
T2-weighted	17.3	17.0	9.2	14.3-20.3	16.0	4-35
SWI/T2*GRE	24.7	29.0	9.0	21.6-27.8	12.0	4-36

Correlation analyses between:				
B. Overall QUASARS scores and patients' characteristics				
	T2-weighted		SWI/T2*GRE	
	T_b	p-value	T_b	p-value
Age at scan	-0.40	0.725	-0.14	0.241
Disease duration	-0.021	0.855	0.064	0.597
C. Overall QUASARS scores and bilateral hearing thresholds				
Both ears 3FA	0.28	**0.018***	0.27	**0.031***
Both ears 4FA	0.29	**0.012***	0.29	**0.019***
D. Haemosiderin appearances CNVIII and ipsilateral hearing thresholds				
Right ear 3FA	0.27	0.055	0.35	**0.017***
Right ear 4FA	0.257	0.065	0.34	**0.021***
Left ear 3FA	0.12	0.394	0.40	**0.006****
Left ear 4FA	0.15	0.294	0.39	**0.007****
E. Haemosiderin appearances Sylvain fissure and ipsilateral hearing thresholds				
Right ear 3FA	0.20	0.147	0.39	**0.007****
Right ear 4FA	0.21	0.135	0.37	**0.01****
Left ear 3FA	0.30	**0.033***	0.25	0.125
Left ear 4FA	0.31	**0.024***	0.23	0.084
F. Haemosiderin appearances CNVIII/Sylvain fissure and ipsilateral hearing thresholds				
Right ear 3FA	0.28	**0.044***	0.41	**0.005****
Right ear 4FA	0.29	**0.035***	0.39	**0.007****
Left ear 3FA	0.292	**0.036***	0.29	**0.045***

Left ear 4FA	0.322	**0.021***	0.31	**0.032***
G. Haemosiderin appearances CNVIII/Sylvain fissure and contralateral hearing thresholds				
Right ear 3FA	0.17	0.214	0.39	**0.007****
Right ear 4FA	0.18	0.197	0.36	**0.014***
Left ear 3FA	0.37	**0.008****	0.32	**0.028***
Left ear 4FA	0.39	**0.006****	0.36	**0.014***

Table 4.3. Overall rating scale scores **(A)** and correlation analyses **(B-G)**. **A**. Rating scale scores were calculated for T2-weighted and susceptibility-weighted imaging (SWI) or T2*-gradient echo (T2*GRE) sequences. Correlation analyses of scores and age or disease duration **(B)** or hearing thresholds **(C)**; correlation analyses of hearing thresholds and corresponding ipsilateral haemosiderin MRI appearance involving CNVIII **(D)** or Sylvian fissure **(E)**, or combined CNVIII/Sylvian fissure **(F),** or contralateral haemosiderin appearance involving CVIII/Sylvian fissure **(G)**. Kendall tau-b correlation coefficient reported (Ƭb); the level of significance was set at 0.05; asymptotic 2-tailed p-values provided.

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Case	Side	4FA	OAE	ART	ABR	Central Auditory F	Auditory segment affected	C	P	vHIT	Caloric	oVEMP	cVEMP	Vestibular segment affected	QUASARS
1	Rt	105			INC		INC‡	X‡	X		X	X	X	Central‡, peripheral	27
	Lt	96.3			INC		INC‡	X‡	X		n	n	X	Central‡, peripheral	
2	Rt	25.5	Pres		Abn		Retro‡	n	n					Normal	32
	Lt	48.8	Abs		Abn		Retro‡ Cochlear‡	n	n					Normal	
3	Rt	62.5		CNVIII/BS	INC		Retro‡ Cochlear INC‡	X	X		n			Central, peripheral	29
	Lt	68.8		CNVIII/BS	INC		Retro Cochlear INC‡	X	X		n			Central, peripheral	
4	Rt	83.8	Abs				INC‡	X‡	n	P SCC		n	n	Central‡, peripheral	32
	Lt	77.5	Abs				INC‡	X‡	X	Central		n	n	Central‡; peripheral	
5	Rt	105	Abs	INC	INC		Cochlear‡ Retro INC‡	n		L SCC‡	X‡		X‡	Peripheral‡	32
	Lt	120	Abs	INC	INC		Cochlear‡ Retro INC‡	n		L SCC‡	X‡		X‡	Peripheral‡	
6	Rt	48.8			Abn		Retro Cochlear INC‡	X	X		n			Central, peripheral	29
	Lt	56.3			INC		Retro INC‡, Cochlear INC‡	X	X		n			Central, peripheral	
7	Rt	23.8					INC‡	n	n	n				Normal	4
	Lt	32.5					INC‡	n	n	n				Normal	
8	Rt	56.3	Abs	CNVIII/BS	INC	Abn	Retro Cochlear‡	X	n	n		n	n	Central	35

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	Lt	42.5	Abs	CNVIII/BS	Abn	Abn	Retro Cochlear‡	X	n	n		n	X	Central, peripheral	
9	Rt	Mod	Abs‡	Cochlear*‡	Abn‡		Cochlear‡ Retro‡								7
	Lt	Sev	Abs‡	INC‡	INC‡		Cochlear‡ Retro INC‡								
10	Rt	12.5	Pres	CNVIII	Abn	Abn	Retro	X	X	P SCC		n	n	Central, peripheral	18
	Lt	10	Pres	n	Abn	Abn	Retro	X	n	Central		n	n	Central	
11	Rt	Profound					INC								22
	Lt	Profound					INC								(T2)
12	Rt	56.6	Abs‡		INC‡	Abn‡	Retro‡	X	X	Central, P SCC		X	X‡	Central, peripheral	29
	Lt	23.8	Pres		Abn‡	Abn‡	Retro‡	X	X	L SCC		n	X‡	Central, peripheral	
13	Rt	10					Normal							Normal*	4
	Lt	6.3					Normal				X			Peripheral*	(T2)
14	Rt	35	Abs‡	INC			Retro Cochlear‡	n	n					Normal^	22
	Lt	61.3	Abs‡	INC			Retro Cochlear‡	n	n					Normal^	
15	Rt	26.3	Abs‡	CNVIII	Abn	Abn	Retro Cochlear‡	X‡	n	Central‡		n	n	Central‡	21
	Lt	10	Abs‡	CNVIII	Abn	Abn	Retro Cochlear‡	X‡	n	Central‡, A SCC		X	n	Central‡, peripheral	
17	Rt	60					INC								31
	Lt	26.3					INC								
18	Rt	50		CNVIII/BS	Abn		Retro Cochlear INC‡	X‡	X	n/a	n		X	Central‡, peripheral	30
	Lt	68.8		CNVIII/BS	Abn‡		Retro Cochlear INC‡	X‡	X	n/a	X		X	Central‡, peripheral	

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#	Side															#
19	Rt	50						INC								20
	Lt	52.5						INC								
20	Rt	12.5	Pres		n			Normal	X‡	n		n			Central‡^^	5
	Lt	15	Pres		n			Normal	X‡	n		n			Central‡^^	(T2)
21	Rt	16.3	Pres		Abn	Abn		Retro Normal cochlear	X	n	Central, L SCC	n/a	n	n	Central, peripheral	32
	Lt	23.8	Pres		Abn	Abn		Retro Normal cochlear	X	n	Central, L/P SCC	n/a	X	n	Central, peripheral	
22	Rt	120						INC‡	X‡	X‡		X‡		n	Central‡, peripheral‡	29
	Lt	120						INC‡	X‡	X‡		X‡		n	Central‡, peripheral‡	
23	Rt	87.5		INC‡	INC‡			INC‡	X‡	X	Central, L/P SCC		n	X‡	Central‡, peripheral	32
	Lt	65		INC‡	INC‡			INC‡	X‡	X	Central, L/P SCC		X	X‡	Central‡, peripheral	
24	Rt	36.3						Cochlear‡ Normal retro	n			n	n	n	Normal^^^	30
	Lt	97.5						Retro‡	n			n	n	X	Peripheral^^^	
25	Rt	20	Abs‡	n	Abn			Cochlear‡ Retro‡	X‡	n					Central‡	8
	Lt	13.8	Abs‡	n	Abn			Cochlear‡ Retro‡	X‡	n					Central‡	
26	Rt	52.5			Abn			Retro, cochlear INC‡	X‡	X	Central, P SCC				Central‡, peripheral	34
	Lt	55			Abn			Retro, cochlear INC‡	X‡	X	Central				Central‡, peripheral	
27	Rt	50						Cochlear‡, normal retro	X	n	Central				Central	13
	Lt	48.8						Cochlear‡	X	n	Central				Central	

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No	Ear														
							Normal retro								
28	Rt	13.8	Pres	n		n	Normal	n	X					Peripheral‡	11
	Lt	7.5	Pres	n		n	Normal	n	X					Peripheral‡	
29	Rt	27.5					INC‡	X	n	Central				Central	20
	Lt	120					INC‡	X	n	Central				Central	
30	Rt	41.3		CNVIII/BS	Abn	Abn	Retro Cochlear INC‡	X‡	X	n/a	X	X‡	n	Central‡, peripheral	33
	Lt	38.8		CNVIII/BS	Abn	Abn	Retro Cochlear INC‡	X‡	X	n/a	X	X‡	n	Central‡, peripheral	
31	Rt	31.3					Cochlear‡ Normal retro	X	n	Central			X‡	Central	10
	Lt	33.8					Cochlear‡ Normal retro	X	n	Central			X‡	Central	
32	Rt	16.3	Pres				Normal Retro INC‡								4 (T2)
	Lt	12.5	Abs				Cochlear Retro INC‡								
33	Rt	33.8					Retro Cochlear INC‡								20
	Lt	45					Retro Cochlear INC‡								
34	Rt	93.8					INC								36
	Lt	91.3					INC								
35	Rt	73.8					INC								20
	Lt	70					INC								
36	Rt	55					INC								20
	Lt	55					INC								

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Table 4.4. Auditory and vestibular findings (adapted from Tables 3.2 and 3.5, Chapter 3) with corresponding QUASARS scores for paramagnetic-sensitive sequences (except in cases marked with (T2) where only T2-weighted images were available). Legend: F function (results from central auditory function tests: Listening in Spatialised Noise-Sentences; Quick Speech-in-Noise); C central and P peripheral gaze/oculomotor/rotatory chair test results. QUASARS SWI scores provided. Please see respective tables for additional legend keys.

4.4 Discussion

This study introduces a simple and reliable measure to radiologically assess for presence of and quantify the anatomical distribution of haemosiderin deposits visualised on MRI.

The study demonstrates excellent reliability of the rating scale. It can be used on either T2-weighted or paramagnetic MRI sequences, irrespective of the level of training of the rater, and can be used in clinical and research settings.

Several studies have previously attempted to quantify the radiological appearance of haemosiderin. These were performed predominantly in the research settings, using the QSM technique which may be technically challenging, require advanced analysis techniques and software and might not be available for use in routine clinical practice (75-77, 313). In contrast, the use of the proposed rating scale (QUASARS) does not require any additional software or advanced technical analyses or training. The time to complete the rating and obtain the score is approximately 10 minutes per scan (for a T2-weighted or paramagnetic sensitive MRI sequence pair).

The findings from this study also confirm the invariable involvement of superior vermis and cerebellar folia, in keeping with the radiological diagnostic criteria. It is likely that these are the earliest structures to demonstrate haemosiderin deposits and thus be involved in iSS. Additionally, the brainstem involvement was evident in the majority of cases, conforming to the findings by Wilson et al (7).

This study also demonstrates that paramagnetic-sensitive imaging is more sensitive for detection of haemosiderin than T2-weighted images, which is in keeping with the

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previous reports on the advantage of the use of paramagnetic-sensitive imaging than T2-weighted sequences (69).

The study demonstrated that QUASARS scores and the appearances of haemosiderin deposits visualised using the paramagnetic-sensitive sequences may correlate with the hearing function. This is also reflected in the correlation between the hearing thresholds and haemosiderin-laden appearances of both CNVIII and Sylvian fissures (ipsilaterally and contralaterally to the hearing function) which is significant as both these areas are known to be the key structures of the auditory pathway, and also consistent with the crossover of the auditory fibres and contralateral representation of the auditory function in the central auditory pathway (19).

The findings of normal vestibular function in 2 cases were not supported by QUASARS scores which were consistent with the extensive haemosiderin deposits infratentorially and also extending supratentorially, suggesting that the vestibular dysfunction may be predated in some iSS individuals by the radiological haemosiderin appearances.

4.4.1 Study limitations

The major limitation to the QUASARS study is the lack of standardised brain imaging due to the variations in MRI acquisition protocols between different units and vendors. The differences that exist between the scanners and the imaging protocols may have led to more heterogenous results than if only one scanner had been used for all the study participants. Other limitations include the retrospective nature of the

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study and limited availability of some of radiological and clinical data, and that the formal assessment of feasibility of the rating scale was not performed.

Similar to the AViSS study, QUASARS is a cross-sectional retrospective study. and accessibility of the imaging was limited in some cases. The rating of the overall cohort (excluding the ratings performed for the reliability analysis) was performed without the rater's being blinded to the clinical details of the patients. The study lacked a control group.

4.5   Conclusion

This is the first study to introduce an iSS imaging rating scale which is a simple tool to measure the radiological appearance of haemosiderin based on its anatomical distribution. This newly developed rating scale appears to have excellent reliability. The rating scale may be a useful tool in the clinical and research settings for the evaluation of haemosiderin appearances at baseline and possibly on interval imaging. However, further studies are needed to determine QUASARS usefulness to monitor disease progression, response to treatment and to correlate the scores with other clinical biomarkers including those of the CSF, as well as cognitive and vestibular functions. It is plausible that early radiological identification of iSS may precede the clinical features – namely the onset of audiovestibular symptoms – however this needs to be studied in the longitudinal studies.

CHAPTER 5   UKB iSS PREVALENCE STUDY

PREVALENCE OF iSS IN THE UK BIOBANK POPULATION

5.1   Introduction

5.1.1   Current iSS prevalence

iSS is considered rare, defined as affecting one per 2 000 in the European population (128, 132). A small number of studies described iSS prevalence to be between 0.03% and 0.14% (81, 86, 139, 140) The prevalence of iSS in the general UK population has not yet been reported.

5.1.2   UK Biobank as a large population health data repository

UK Biobank (UKB) data repository is a dedicated health repository study in which clinical, social, demographics and imaging data were collected from a large sample of general UK population (190).

It was hypothesised that by reviewing the imaging data from a large sample of the UKB participants, and by identifying the cases with the radiological features of suggestive of iSS, the prevalence of iSS can be estimated (185, 186, 190, 298, 314).

5.1.3   Study aims

The aim of this study is to estimate the prevalence of iSS, based on the pre-defined radiological criteria, in a large sample from the general UK population (7).

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5.2 Methods

5.2.1 UK Biobank data access and Ethical permissions, and data compliance

The UKB repository study was commenced following the permission granted by the Research Ethics Committee (298). The permission to access the UKB data was granted by the UKB team (Project 16256). Detailed description of the study permissions from the Research Ethics Committee and from the UKB Access Committee, and the data compliance are described in Chapter 2.

5.2.2 Study design, population, and setting

This is a cross-sectional observational study based on the brain MR imaging data obtained from the UKB which had been collected from a large UK population sample, aged 40-69 (190). The UKB imaging data were accessed to review paramagnetic-sensitive (SWI) MR brain images (3 Tesla field strength from the identical scanners and using the same scanning parameters). The imaging data were downloaded from the UKB server, in the order provided by the UKB.

Study inclusion criteria: MR images of the brain with paramagnetic-sensitive sequence (SWI) of the participants from UKB study.

Study exclusion criteria: incomplete scans such that did not allow full visualisation of all anatomical regions included in QUASARS or scans with severe motion artefact, defined as appearance of concentric circles unreliable for image interpretation (315).

All the images were viewed by the researcher (NK) in a darkened room, using a high-resolution screen.

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5.2.3 Statistical analysis

The prevalence was calculated using the following formula (Chapter 2) (304, 305):

$$\text{Prevalence (\%)} = \frac{\text{cases identified}}{\text{total number of cases}} \times 100$$

The estimated confidence intervals were calculated using the Wilson Score method, as described in Chapter 2 (304-306). The identified cases and the description of the radiological findings were tabulated. The QUASARS scores were calculated for each such case, and also tabulated.

5.3 Results

In total, 10 341 MRI cases were reviewed as part of this study. Severe motion artefact was identified in 35 cases which were not included in the analysis.

5.3.1 Imaging features of identified cases

Of the 10 306 cases included, 5 cases had radiological features suggestive of iSS. The haemosiderin distribution of the identified cases including their overall QUASARS scores are described in **Table 5.1.** Haemosiderin was observed to involve superior cerebellar vermis and cerebellar folia in all identified cases **(Figure 5.1)**, as outlined in the radiological diagnostic criteria (7).

In Case 4, the signal dropout suggestive of haemosiderin deposits was observed to involve superior vermis bilaterally, yet the cerebellar folia involvement was unilateral. The case, however, was included as the likely radiologically confirmed iSS because: (a) the appearances of the signal dropout were similar to those observed in the clinical cohort in the QUASARS study; (b) the involvement of superior vermis was

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symmetrical; (c) in view of thick slices (3mm) used in the UKB SW MRI image acquisition which may have failed to demonstrate the involvement of the right-sided cerebellar folia in this case. Furthermore, in this case (Case 4), the findings were suggestive of additional involvement of all supratentorial regions, with symmetrical appearances of signal dropout suggestive of haemosiderin deposits **(Figure 5.2),** and as described in QUASARS.

Case number	SWI MRI findings	QUASARS
Case 1	Superior vermis bilaterally Cerebellar folia bilaterally	4
Case 2	Superior vermis bilaterally Cerebellar folia bilaterally	4
Case 3	Superior vermis bilaterally Cerebellar folia bilaterally	4
Case 4	Superior vermis bilaterally Cerebellar folia left Full supratentorial involvement bilaterally	23
Case 5	Superior vermis bilaterally Cerebellar folia bilaterally	4
Extra case*	Superior vermis left only	1

Table 5.1. Description of haemosiderin appearances in the identified cases visualised on the paramagnetic-sensitive (SWI) MRI and corresponding QUASARS scores. *This case was deemed equivocal with regards to the radiological features of iSS; the findings are included for illustrative purposes only.
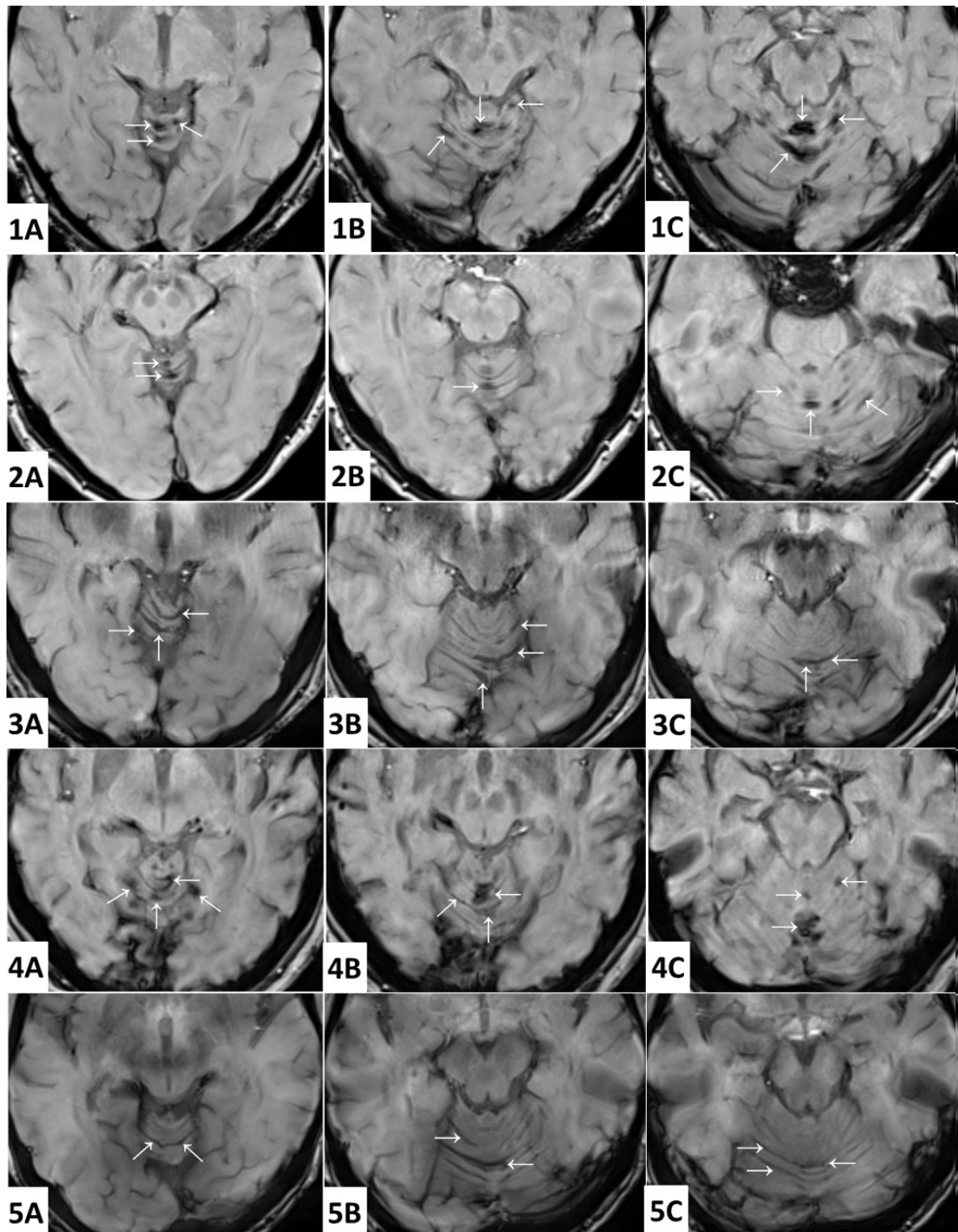
Figure 5.1. Axial susceptibility weighted magnetic resonance images of the identified cases. Appearances of the signal dropout suggestive of haemosiderin deposits are marked with arrows. Each case is numerically represented (1-5); A-C: cephalad to caudal images of superior vermis and cerebellar folia provided for each case. Images: © UK Biobank.

In one further case (Extra Case, **Table 5.1, Figure 5.3**), the signal dropout suggestive of haemosiderin deposits was visualised in the left superior vermis only, without any additional evidence of the involvement of infratentorial regions, and was deemed equivocal (7).

5.3.2 <u>iSS prevalence in the studied sample</u>

Based on these findings, the prevalence of iSS was calculated as the proportion of 5 of 10 306 cases reviewed, $\rho = 0.000\,485\,154$, which equals to 0.0485% (95% CI 0.0207 to 0.114) or 48.5 per 100 000 population.

5.4 Discussion

This is the first study to report the prevalence of iSS in a large cohort of individuals representing a cross-sectional sample from the general UK population, with the participants' age range being similar to the age range at which iSS may be diagnosed (8). It is also probably the largest study to date to describe iSS prevalence in a non-hospital population.

The study's findings suggest that iSS might not be as rare as previously hypothesised, albeit still, the estimated prevalence of 48.5 per 100 000, falling just within the range of the definition of a rare disease which is defined as affecting 5 per 10 000 individuals (or 50 per 100 000) in a European population (132). The study's findings are also similar to the prevalence of iSS identified in other studies **(Table 5.2, Figure 5.4)** (81, 86, 139, 140).
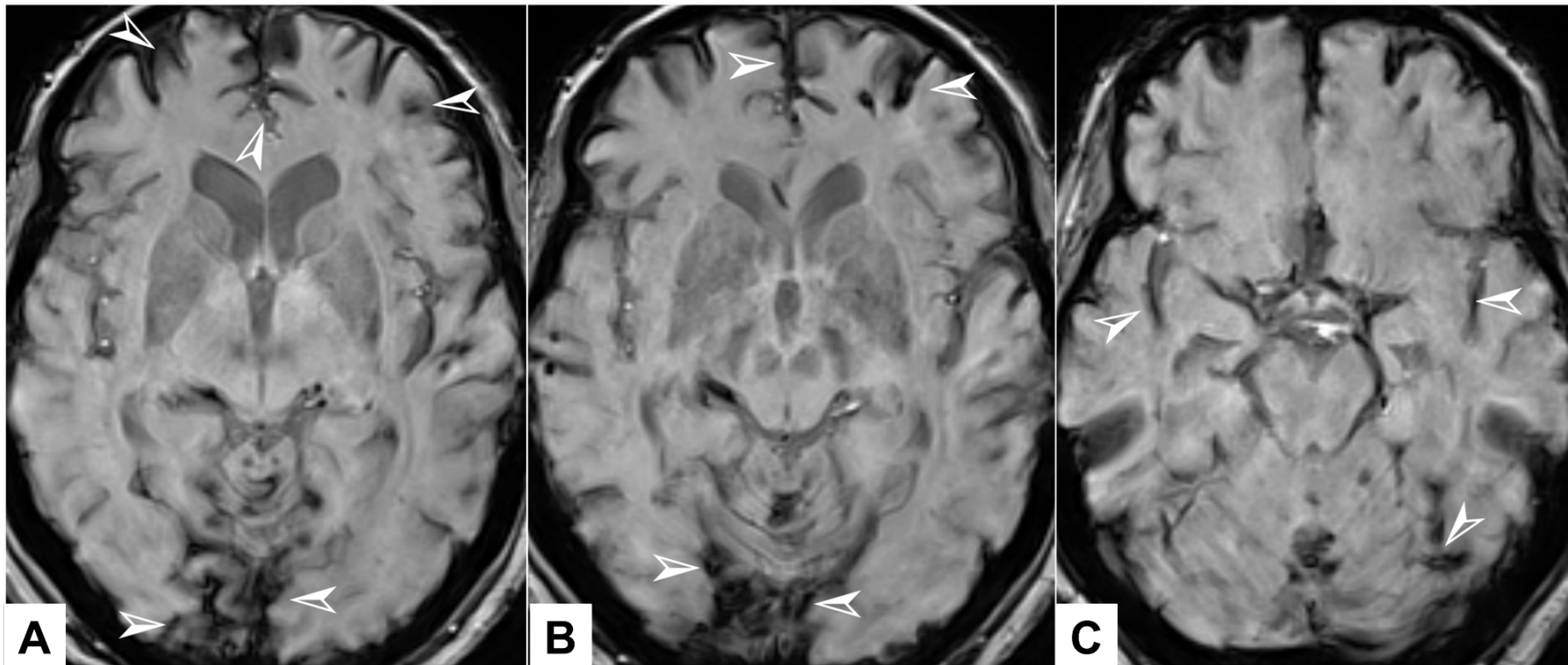
Figure 5.2. Axial susceptibility weighted magnetic resonance images of the supratentorial involvement in Case 4. Appearances of signal dropout suggestive of haemosiderin deposits are marked with arrowheads. A-C: cephalad to caudal images provided. Images: © UK Biobank.
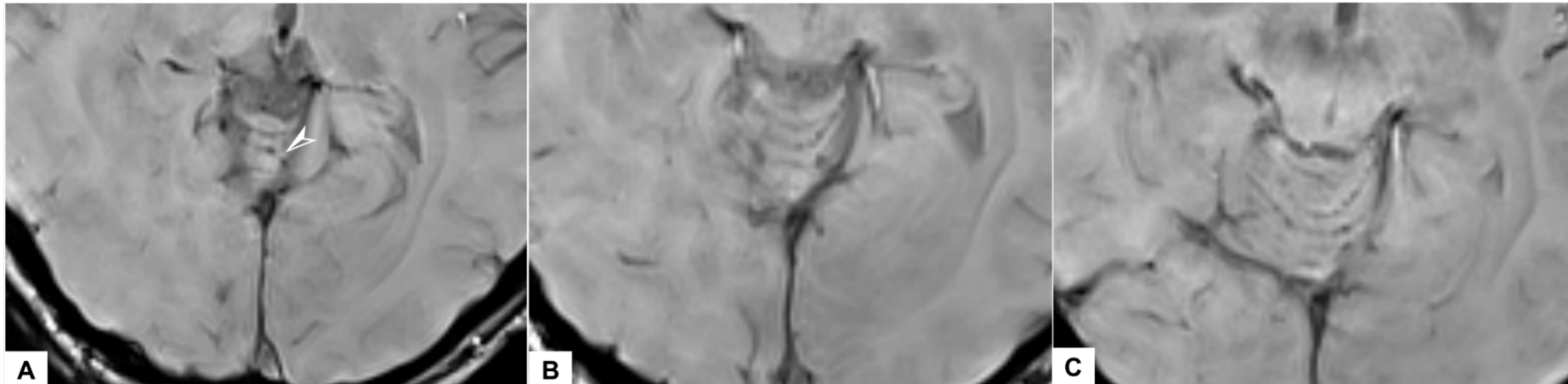
Figure 5.3. Axial susceptibility weighted magnetic resonance images of the case that was deemed equivocal. Here, the findings suggest presence of siderosis involving the left superior vermis only (**A**, arrowhead); **A-C**: cephalad to caudal images of superior vermis and cerebellar folia. Images: © UK Biobank.

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Referenced study	MRI parameters	Findings	Percent prevalence (95% CI)	Prevalence per 100 000
Vernooij (139)	1.5T T2*GRE	1/1062	0.0942 (0.0166-0.5314)	94.2
Pichler (86)	3T T2*GRE	2/1412	0.1416 (0.0389-0.515)	141.6
Offenbacher (81)	1.5T T2-weighted; T2*GRE	9/8843	0.1018 (0.0536-0.193)	101.8
Friedauer (140)	T2-weighted; T2*GRE/SWI‡	30/97 733	0.0307 (0.0215-0.0438)	30.7
Current study	3T SWI	5/10 306	0.0485 (0.0207-0.114)	48.5
Pooled findings	n/a	47/119 356	0.0394 (0.0296-0.0523)	39.4

Table 5.2. Study findings in the context of the findings of iSS prevalence from other studies. Legend: ‡field strength not stated; CI confidence intervals; GRE gradient recalled echo; MRI magnetic resonance imaging; n/a not applicable; SWI susceptibility-weighted imaging; T Tesla.

iSS study comparison
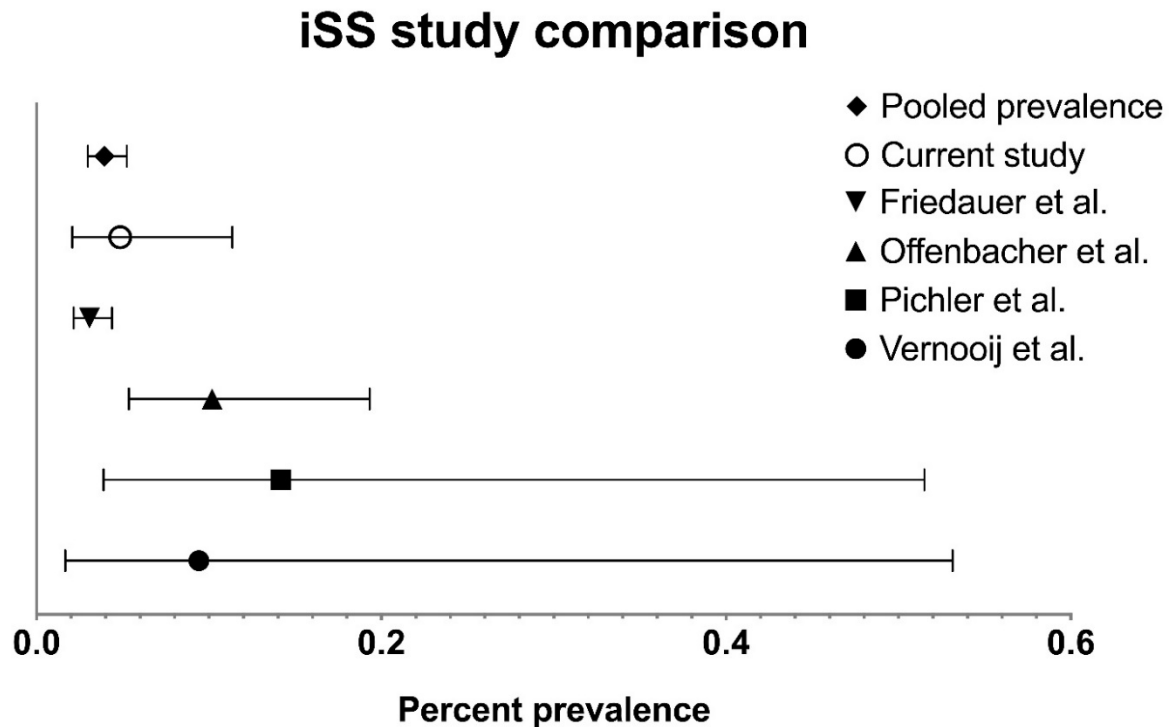
Figure 5.4. Between-studies comparison of iSS prevalence (mean with error bars). The figure includes the findings from the current study and pooled prevalence (81, 86, 139, 140).

Condition/disease	Prevalence per 100 000	Percent prevalence	Population, country
ALS	4.4	0.004	USA (316)
CANVAS	5	0.005	European, UK (317)
SCA (most to least common): SCA3, SCA2, SCA 6, SCA 7	1-5 0.9-3	0.001-0.005	Global (318, 319) European (320)
Friedreich's ataxia (FRDA)	0.3-5	0.0003-0.005	European (321)
Vestibular schwannoma	12-42	0.012-0.042	USA (322), USA (323)

Table 5.3. Prevalence of several rare neuro-otological disorders which can be encountered the dedicated clinics. Legend: ALS Amyotrophic lateral sclerosis, CANVAS Cerebellar ataxia with neuropathy and vestibular areflexia syndrome; SCA Spinocerebellar ataxia.

5.4.1 <u>Study limitations</u>

There are several potential limitations to this study. It has been previously argued that the cohort of individuals who took part in the UKB study might not be representative of the general population in the UK due to possible sampling bias (324). This has been explored in a dedicated study which demonstrated that the participants in UK Biobank tend to differ in lifestyle, with better health-related parameters compared to the general UK population (325). It is thus likely that this study might be less accurate in estimating the prevalence of iSS in the general UK population. Furthermore, due to the age range of the UKB population sample, the prevalence may be different if younger (< 40 years old) or older (≥ 70 years old) populations are included.

Due to the technical challenges with UKB data download, the radiological findings of the identified cases could not be assessed against the clinical data on the auditory and vestibular functions of these participants.

The images were reviewed manually (one by one) which may have resulted in some cases having been missed and thus not reported in the analysis. Therefore, automated analysis may be introduced in the future studies of this kind to identify cases suggestive of the radiological findings of iSS. Automated analysis may offer greater precision, minimise the risk of cases being missed and increase the speed of data analysis thus undertaken in shorter time (i.e., shorter time-frame during which the study is undertaken) and thus have the potential to increase the sample size – to include all the brain MRI studies available in the UKB database (currently 50 000) (200).

5.5   Conclusion

This is the first population-based study to estimate the prevalence of iSS in a large

UK sample. The prevalence of iSS appears to be comparable to other rare neuro-

otological conditions which can be encountered in the AVM, Neuro-otological, ENT

or audiology or balance clinics.

CHAPTER 6   QoL in iSS and ARHL STUDY

ASSESSMENT OF AUDITORY FUNCTION AND HEALTH-RELATED QUALITY OF LIFE IN INDIVIDUALS WITH INFRATENTORIAL SUPERFICIAL SIDEROSIS AND WITH AGE-RELATED HEARING LOSS USING PATIENT-REPORTED OUTCOME MEASURES

6.1   Introduction

The importance of assessing health-related quality of life (HRQoL) in rare diseases has been emphasised and deemed a research priority (326). The use of patient-reported outcome measures (PROMs) in the clinical and research settings has been growing. PROMs can quantitatively assess the impact of the condition on the individuals' health and health-related quality of life (HRQoL). Such measures can evaluate the person's experience of living with a specific disease or estimate its impact on a specific function.

Generic HRQoL PROMs that include a hearing domain in the individuals in whom hearing loss is common may better capture HRQoL (166).

The use of dedicated hearing-specific PROMs can provide additional information regarding the auditory profile of the individuals with hearing loss due to a specific disorder or condition (171).

It was hypothesised that salient auditory characteristics of iSS exist which may be reflective of the impairment of specific segment along the auditory pathway, and that these salient features can be identified through hearing-specific PROMs and which in turn can help identify features differentiating iSS-related hearing loss from ARHL.

This can add to the current body of knowledge regarding the auditory function in individuals with iSS and help inform clinicians of the likely auditory deficits in this population and thus provide more specific hearing rehabilitative strategies in this population.

Furthermore, the impact of hearing loss on HRQoL in individuals with iSS may be significant in view of the hearing loss being the most prevalent clinical feature of iSS. The assessment of HRQoL has not been performed for iSS to date.

6.1.1 Aims

The aims of this study were to determine: (1) the overall HRQoL scores for individuals with iSS and with ARHL using two common generic HRQoL PROMs; (2) the worst affected domains in HRQoL measures in both groups; (3) the auditory profile in both groups using hearing-specific PROMs and (4) whether iSS-specific auditory characteristics exist that are different from ARHL characteristics - by comparing iSS and ARHL auditory profiles derived from hearing-specific PROMs from individuals in these groups.

6.2 Methods

6.2.1 Study design, population and setting

This is a prospective observational cross-sectional study undertaken as an anonymised online survey which included study-specific questions, two validated generic HRQoL questionnaires and four hearing-specific questionnaires (including one on tinnitus), presented in fixed order. Dedicated organisations and charities were contacted to distribute information about the study to their members and inviting their

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members who had been diagnosed with classical superficial siderosis or with age-related hearing loss – to participate in the study. The delivery of the survey as well as study data collection were performed using the UCL licenced REDCap platform.

To take part in the study, the potential participants needed to confirm that they were at least 18 years old, had been diagnosed with iSS or ARHL, and provided formal consent. Only then they were able to proceed to the survey webpages. Full details regarding participants' inclusion and exclusion criteria, recruitment and consent procedures are described in Chapter 2.

The participants were asked to indicate their hearing levels, as advised by their hearing specialist, and also indicate if they had tinnitus and its severity if present.

The following questionnaires were included in the study (number of domains, worst-best scores range):

Generic HRQoL questionnaires:

- HUI3: 8 domains, -0.36 to 1;

- EQ5D-5L: 5 domains; -0.594 to 1;

Hearing-specific questionnaires:

- mAIADH: 5 domains, 0 to 3;

- SSQ: 3 domains; 0 to 10;

- ERSA: 4 domains (0 to 50 (each domain) or 0 to 150 (total score, excluding occupational domain scores);

- TFI: 8 domains; 100 to 0.

6.2.2 Statistical analysis

Sample size calculations were not performed prior to commencing the study, due to the rarity of iSS and its unknown prevalence, with the view to have the largest study sample possible. The responses were reviewed; duplicate and incomplete entries were excluded from the analysis.

In addition to the statistical analyses described in Chapter 2, the following analyses were performed (SPSS Versions 26, 27 and 28, IBM Armonk, NY). To assess for difference between the instrument scores while controlling for hearing levels, non-parametric Quade's analysis of co-variance (ANCOVA) was used (327). Post-hoc analyses were not deemed necessary because there were fewer than 3 groups in the Quade's ANCOVA.

6.3 Results

6.3.1 Participants' characteristics

Data on 50 participants from iSS group were available for analysis. Their demographic and iSS specific characteristics were described in detail in "Health-related quality of life in adults with classical infratentorial superficial siderosis: a cross-sectional study" (74). Of 50 participants, three reported no hearing problems, therefore the analysis of the data on 47 iSS participants with hearing difficulties was analysed for the purposes of this study. Data on 30 participants in ARHL group were analysed as part of this study.

The participants' characteristics are presented in **Table 6.1** and **Figure 6.1**. The hearing levels and tinnitus thresholds are reported for the worse ear.

Values (n, %)	ISS group (n=47)					ARHL group (n=30)				
Gender (males)	28 (60%)					12 (40%)				
	mean	median	SD	95% CI	IQR	mean	median	SD	95% CI	IQR
Age at survey	57.5	59.0	12.1	54.0-61.1	15	74.6	75.0	7.9	71.7-77.6	10
Age at onset of hearing problems	44.8	47.0	16.5	39.8-49.7	21	62.0	61.0	9.2	58.5-65.4	11
Duration of hearing symptoms (years)	13.7	9.0	14.4	9.4-18.1	12.5	12.7	10.0	7.9	9.7-15.6	11.3
Hearing difficulties (including in background noise)	Yes 47 (100%) Sometimes 3 (6%)‡					Yes 30 (100%) Sometimes 4 (13%)‡				
Tinnitus present	Yes 37 (79%), of which unilateral 8 (17%)					Yes 8 (27%), of which unilateral 1 (3%)				

Table 6.1. Participants' demographics and hearing-specific characteristics by group. Legend: CI confidence intervals; SD standard deviation; IQR interquartile range; ‡participants indicated they sometimes had hearing difficulties in background noise.
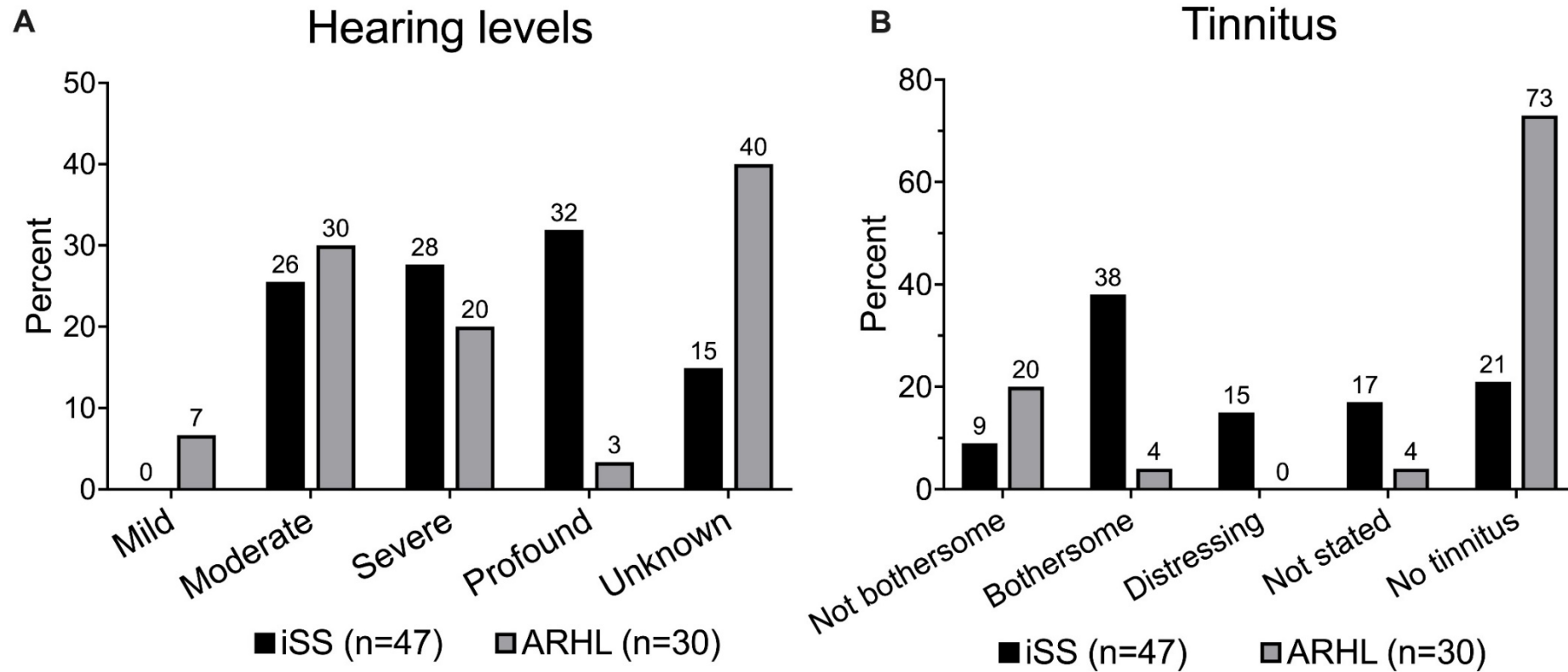
Figure 6.1. Participants' reported hearing levels (A) and tinnitus (B) for each group. Hearing levels and tinnitus severity are reported for worse ear; ARHL age-related hearing loss; CI confidence intervals; IQR interquartile range; iSS infratentorial superficial siderosis; SD standard deviation. The percent values provided do not add up to 100% due to rounding to the nearest whole number.

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6.3.2 Total and sub-scores for generic HRQoL and hearing specific measures

The overall scores for the generic HRQoL and hearing-specific measures, including the sub-scores of their domains are reported in **Table 6.2.** The scores for the HUI3 hearing domain appear to be the worst for both groups.

6.3.3 Between-group comparison of participants characteristics

The between-group comparison of the parameters such as age, hearing levels and duration of hearing symptoms are reported in **Table 6.3**. The participants from the iSS group were younger than the ARHL group, which was statistically significant (U=1018, z=3.27; p=0.001). Participants in the iSS group also had worse hearing levels, despite being younger than the participants in the ARHL group (U=197.5, z=-2.88; p=0.004), and had worse tinnitus severity than the ARHL group participants (U=37.5; z=-2.69, p=0.007). There was no statistically significant difference in duration of the hearing symptoms between the two groups **(Table 6.3)**.

6.3.4 Between-group comparison of scores from generic HRQoL and hearing-specific measures

The between-group comparison of the total scores and sub-scores for hearing-specific and generic HRQoL measures are reported in **Table 6.3**. Analysis of the scores unadjusted for hearing levels demonstrated statistically significantly worse scores for the iSS group than for ARHL group for HUI3 (including hearing domain) and EQ5D multi-attribute scores as well as EQ5D VAS. The scores were also worse for the participants in the iSS group across all hearing-specific measures, likely due

to significantly worse hearing levels reported by the participants in this group than in the ARHL group.

Non-parametric Quade's analysis of covariance (ANCOVA) allowed to assess for difference in the instrument scores between the two groups while controlling for hearing levels (**Table 6.3**). This analysis demonstrated no statistically significant difference in SSQ total or sub-scores, or total mAIADH scores between the groups ($p > 0.05$). The statistically significant difference between the groups was identified for mAIADH sub-scores for the following domains: sound recognition ($p < 0.001$) and localisation ($p = 0.046$); the sub-scores were worse for the iSS group (**Table 6.3**). The statistically significant difference ($p < 0.05$) was also present between the groups for the ERSA total and sub-scores (except for the personal life domain) and for the TFI total and sub-scores (except for the cognitive and emotional distress domains).

6.4   Discussion

This is the first study to determine the auditory profile of the individuals with iSS using hearing-specific PROMs and compare it to the auditory profile of the individuals with ARHL. The results of this study show that the iSS participants, despite being younger than the participants in the ARHL group, had significantly worse hearing levels compared to the ARHL group. The worse hearing levels of the participants in the iSS group were likely to have been reflected in the scores across all hearing-specific instruments which were worse for that group than the scores for the ARHL group.

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Instruments	iSS group						ARHL group					
mAIADH scores	N	mean	median	SD	95% CI	IQR	N	mean	median	SD	95% CI	IQR
mAIADH TOTAL	47	1.5	1.4	0.8	1.3-1.8	1.3	30	2.2	2.3	0.5	2.1-2.4	0.7
Speech-in-noise	47	0.96	0.8	0.8	0.7-1.2	1.0	30	1.6	1.8	0.8	1.4-1.9	0.9
Speech-in-quiet	47	1.6	1.8	1.0	1.3-2.0	1.8	30	2.2	2.4	0.7	2.0-2.5	0.7
Sound localisation	47	1.3	0.8	1.1	1.0-1.6	2.2	30	2.2	2.3	0.7	1.9-2.4	0.9
Sound recognition	47	1.8	1.8	0.9	1.6-2.1	1.5	30	3.0	3.1	0.6	2.8-3.2	0.5
Sound detection	47	1.7	1.6	0.9	1.4-1.9	1.4	30	2.4	2.4	0.5	2.2-2.6	0.8
SSQ scores	N	mean	median	SD	95% CI	IQR	N	mean	median	SD	95% CI	IQR
SSQ TOTAL	44	4.5	4.4	2.2	3.9-5.2	3.4	30	5.9	6.2	1.3	5.4-6.4	1.6
Speech	47	3.7	3.4	2.4	3.0-4.4	3.1	30	4.9	4.7	1.9	4.2-5.6	3.1
Spatial	44	4.0	3.6	2.6	3.2-4.7	4.1	30	5.7	5.7	1.6	5.1-6.3	2.6
(Other) qualities of hearing	44	5.7	6.0	2.3	5.0-6.4	3.3	30	6.8	7.0	0.9	6.5-7.2	0.9
ERSA scores*	N	mean	median	SD	95% CI	IQR	N	mean	median	SD	95% CI	IQR
ERSA TOTAL	43	79.6	84.0	37.4	68.1-91.1	56.0	30	112.3	116.5	22.1	104.1-120.6	35.0
Quality of life	43	29.5	31.0	11.6	25.9-33.1	19.0	30	40.4	41.0	6.1	38.2-42.7	10.0
Personal life	44	25.7	28.0	14.0	21.4-29.9	24.0	30	34.9	36.5	9.5	31.4-38.5	15.5
Social life	44	24.6	26.5	13.9	20.3-28.8	20.3	30	37.0	40.0	8.6	33.8-40.2	13.0

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Occupational life	13	30.2	33.0	9.8	24.3-36.1	13.5	4	43.8	43.0	5.2	35.5-52.0	9.8
TFI scores	**N**	**mean**	**median**	**SD**	**95% CI**	**IQR**	**N**	**mean**	**median**	**SD**	**95% CI**	**IQR**
TFI TOTAL	31	49.1	56.0	22.9	40.7-57.5	38.0	7	11.3	9.6	6.7	5.2-17.5	10.8
Intrusiveness	31	53.6	56.7	21.7	45.6-61.5	33.3	8	19.2	13.4	13.7	7.8-30.6	24.2
Sense of control	34	56.9	56.7	25.3	48.0-65.7	46.7	8	22.9	18.3	21.1	5.2-40.7	36.7
Cognitive function	34	40.4	40.0	27.2	30.9-49.9	44.2	8	16.7	10.0	18.5	1.2-32.2	22.5
Sleep	34	47.6	45.0	32.8	36.1-59.0	58.3	8	6.3	5.0	7.0	0.4-12.1	12.5
Auditory function	34	48.8	51.7	32.5	37.5-60.2	61.7	7	7.1	10.0	7.1	0.6-13.7	13.3
Relaxation	34	53.5	65.0	33.6	41.8-65.3	61.7	7	13.3	10.0	12.6	1.7-25.0	23.3
Quality of life	34	37.4	40.0	28.5	27.5-47.4	56.3	7	5.0	7.5	4.8	0.6-9.4	10.0
Emotional distress	34	31.2	21..7	31.7	20.1-42.3	54.2	7	9.5	10.0	8.5	1.7-17.4	16.7
HUI3 scores	**N**	**mean**	**median**	**SD**	**95% CI**	**IQR**	**N**	**mean**	**median**	**SD**	**95% CI**	**IQR**
HUI3 TOTAL	47	0.33	0.32	0.31	0.24-0.42	0.53	30	0.70	0.74	0.23	0.61-0.79	0.32
Vision	47	0.90	0.95	0.16	0.86-0.95	0.0	30	0.95	0.95	0.04	0.93-0.96	0.0
Hearing	47	0.55	0.71	0.36	0.45-0.66	0.54	30	0.74	0.86	0.24	0.65-0.83	0.21
Speech	47	0.91	1.0	0.16	0.86-0.96	0.18	30	0.97	1.0	0.09	0.94-1.0	0.0
Emotion	47	0.86	0.91	0.20	0.80-0.92	0.27	30	0.95	1.0	0.08	0.92-0.98	0.09
Pain	47	0.81	0.77	0.17	0.77-0.86	0.15	30	0.96	1.0	0.07	0.93-0.99	0.08
Ambulation	47	0.73	0.83	0.26	0.65-0.80	0.33	30	0.95	1.0	0.12	0.90-0.99	0.0

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	N	mean	median	SD	95% CI	IQR	N	mean	median	SD	95% CI	IQR
Dexterity	47	0.90	1.0	0.17	0.85-0.95	0.12	30	0.97	1.0	0.08	0.94-1.0	0.0
Cognition	47	0.77	0.86	0.24	0.70-0.84	0.30	30	0.93	1.0	0.11	0.89-0.97	0.08
EQ5D scores	**N**	**mean**	**median**	**SD**	**95% CI**	**IQR**	**N**	**mean**	**median**	**SD**	**95% CI**	**IQR**
EQ5D TOTAL	47	0.57	0.60	0.26	0.50-0.65	0.33	30	0.84	0.84	0.16	0.78-0.90	0.26
EQ5D VAS	47	58.1	55.0	23.5	51.2-65.0	40	29	77.4	80.0	15.8	71.4-83.4	17.5

Table 6.2. Summary of the results from all instruments (including total and sub-scores) for each group. Legend: CI confidence intervals; EQ5D EuroQOL-5D-5L; HUI3 Health Utilities Index Mark III; IQR interquartile range; mAIADH modified Amsterdam Inventory for Auditory Disability and Handicap; SD standard deviation; T tinnitus; VAS visual analogue scale; *total score out of 150 includes scores for QoL, Personal Life and Social Life domains, total score out of 200 (/200) not calculated.

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A. PARTICIPANTS CHARACTERISTICS	Mean ranks		Mann-Whitney U	
	ARHL	iSS	z-score	p-value
Age	49.4	32.3	3.27	**0.001****
Duration of hearing symptoms	40.3	36.5	0.74	0.458
Hearing levels	20.5	33.6	-2.88	**0.004****
Tinnitus severity	9.4	20.7	-2.69	**0.007****

B. INSTRUMENT SCORES					Quade's ANCOVA	
Hearing-specific instruments	Mean ranks		Mann Whitney U			
	ARHL	iSS	z-score	p-value	F-score	p-value
mAIADH TOTAL	50.8	31.5	3.68	**<0.001****	3.18	0.080
SiN	50.3	31.8	3.54	**<0.001****	1.07	0.307
SiQ	47.3	33.7	2.62	**0.009****	1.88	0.176
Sound localisation	50.7	31.3	3.68	**<0.001****	4.182	**0.046***
Sound recognition	56.4	27.9	5.48	**<0.001****	19.09	**<0.001****
Sound detection	50.2	31.8	3.53	**<0.001****	2.90	0.094
SSQ TOTAL	46.8	31.1	3.08	**0.002****	1.115	0.296
Speech	46.6	34.2	2.38	**0.017***	0.523	0.473
Spatial	46.8	31.2	3.06	**0.002****	0.999	0.322
Qualities	45.0	32.4	2.47	**0.014***	0.439	0.511
ERSA TOTAL (/150)	48.4	29.0	3.85	**<0.001****	5.10	**0.028***
QoL	49.2	28.5	4.09	**<0.001****	8.24	**0.006****
Personal life	46.0	31.7	2.80	**0.005****	0.97	0.330
Social life	49.0	29.7	3.80	**<0.001****	4.78	**0.033***
Occupational life	14.5	7.3	2.50	**0.012***	8.17	**0.014***

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	ARHL	iSS	z-score	p-value	F-score	p-value
TFI TOTAL	6.6	22.4	-3.39	**0.001****	12.54	**0.001****
Intrusiveness	7.8	23.2	-3.41	**0.001****	11.67	**0.002****
Sense of Control	10.0	24.2	-2.95	**0.003****	7.30	**0.011***
Cognitive	12.9	23.5	-2.22	**0.027***	4.0	0.053
Sleep	9.25	24.38	-3.16	**0.02***	13.99	**0.001****
Auditory	8.71	23.5	-2.99	**0.03***	10.70	**0.002****
Relaxation	10.21	23.22	-2.63	0.09	6.96	**0.012***
QoL	10.9	23.1	-2.48	**0.013***	6.343	**0.017***
Emotional distress	15.7	22.1	-1.30	0.195	1.92	0.175
Generic HRQoL instruments	**ARHL**	**iSS**	**z-score**	**p-value**	**F-score**	**p-value**
EQ5D TOTAL	54.7	29.0	4.93	**<0.0001****	15.97	**<0.001****
EQ5D VAS	49.7	31.6	3.47	**0.001****	5.39	**0.024***
HUI3 TOTAL	54.6	29.1	4.88	**<0.0001****	14.04	**<0.001****
HUI3 Hearing domain	45.7	34.8	2.12	**0.034***	0.26	0.616

Table 6.3. Between-group comparison of: participants' characteristics, total and sub-scores from hearing-specific and generic HRQoL PROMs. Analysis was performed using non-parametric Mann-Whitney U (z-scores provided) (301), and using non-parametric Quade's analysis of covariance ANCOVA to control for hearing levels (F-scores provided) (327). Significance level was set at 0.05; asymptotic 2-tailed p-values reported. Legend: * p-value significant at 0.05 level; ** p-value significant at 0.01 level.

The analysis of the mAIADH sub-scores identified the lowest (median) scores in the speech-in-noise domain for both groups, likely reflected in the common complaint of hearing difficulties in the presence of background noise. The scores, however, for the iSS group. were also low (median) in the domain of sound localisation followed by the sound detection domain scores. Comparison of the mAIADH sub-scores between the two groups while controlling for hearing levels identified the worse scores for the iSS group in the sound recognition and sound localisation domains. It is plausible to be the distinguishing feature of iSS-related hearing loss if compared to ARHL – in addition to the hearing thresholds likely to be worse in individuals with iSS than age-matched individuals (13, 43). The hearing impairment in the domain of poor sound localisation may manifest as poor performance in complex auditory environments (328). Poor sound recognition may present as difficulties with following verbal instructions (328).

The hearing impairment in the domains of sound localisation and recognition in the iSS group may also be reflective of the central auditory processing deficits (330, 331). Involvement of these auditory domains has been demonstrated in patients with the formal diagnosis of auditory processing disorder (APD) who completed mAIADH questionnaire (329). The mAIADH (and SSQ) total scores have also been shown to correlate with the psychoacoustic measures in clinical APD patients (170). The involvement of the four (of five) mAIADH domains, namely speech intelligibility in noise and in quiet, sound localisation, and recognition was identified in individuals with APD by Spyridakou et al (330). Difficulties in sound localisation and recognition were also identified in patients with stroke of the auditory brain, and the scores were

shown to correlate with the objective measures assessing central auditory

processing deficits in the studied population (331, 332).

Central auditory processing deficits were indeed identified in the AViSS study

(Chapter 3 of this work) – in several of the iSS participants who underwent dedicated

central auditory processing testing, with the central auditory findings also described

in a dedicated case report (43).

The results of this study also demonstrate the lowest ERSA scores in the personal

and social domains for both groups suggesting that hearing impairment may

negatively impact both personal and social aspects of life in the affected individuals.

The scores were worse however in the QoL, social life and occupational domains for

the iSS group even after controlling for hearing levels.

This study also demonstrated that tinnitus was more prevalent and more severe in

the iSS group than in the ARHL group; this was likely to have been reflected in the

worse TFI scores in the iSS group (except for the cognitive and emotional distress

domains), and possibly demonstrating a greater burden of tinnitus for the participants

in this group.

This study also provides the multi-attribute scores representing the overall HRQoL in

individuals with this rare neurological condition assessed using two common generic

HRQoL measures. The study shows markedly reduced multi-attribute scores for

HUI3 and EQ5D in the iSS group. The impact of iSS on HRQoL has been assessed

as part of the study and described in detail elsewhere (74). These results provide the

evidence to support the need for resource allocation for the iSS-related clinical and

research activities, and may potentially be used to assess for disease progression or

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treatment outcomes, although this should be further evaluated in dedicated studies and validated against clinical and radiological parameters.

6.4.1 Study limitations

There are several study limitations some of which are inherent to its design. The anonymous nature of the study did not allow to verify the participants' diagnoses of iSS or ARHL; the self-reported hearing levels could not be verified.

The delivery of the study may have introduced several bias including order bias as the study-specific questions and the questionnaires were presented in fixed order. This was done in the anticipation of increasing attrition with duration of the survey (the overall completion time of the survey was approximately one hour), and therefore the most common and the shortest questionnaires were presented first. The study delivery and participation required the participants to have access to a digital device which needed to be connected to the internet. This may have limited the participation of the individuals without such facilities. Due to the study design, the scores obtained from the PROMs in this study populations could not be compared to the objective clinical measures of the participants iSS or with ARHL, and this may be the focus of future research.

The study was conducted during the COVID-19 pandemic, and this may have impacted the HRQoL scores observed in this study.

6.5 Conclusion

This study provides baseline measurements of HRQoL and hearing-specific PROMs for the individuals with iSS. The study findings also suggest the presence of central

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auditory deficits which may be a feature of iSS-related hearing impairment. The PROMs utilised in this study may be considered for use alongside the clinical markers at the time of diagnosis (baseline measure) in this group of patients. The PROMs may also be considered as a means to monitor response to treatment or disease progression over time however their role in correlation with the objective clinical measures and in determining clinically significant change in this population have not yet been studied and may be the focus of future research.

CHAPTER 7   GENERAL DISCUSSION AND SUMMARY

This chapter provides an overall review of the completed work, summary of the findings, describes the clinical implications of the project's results and proposes directions for future research.

This project comprises several studies which investigate the role of the clinical auditory, vestibular, and imaging biomarkers, as well as self-reported measures in evaluating the auditory and vestibular functions in a rare neuro-otological condition – classical infratentorial superficial siderosis. This project also investigates the prevalence of the olfactory dysfunction in a cohort of patients with this condition and estimates the prevalence of iSS in a general UK population sample.

The findings from the first research study (AViSS study, laid out in Chapter 3), obtained from a relatively large sample of individuals with iSS, contribute to the current pool of knowledge regarding the iSS-related auditory and vestibular phenotype and concur with the current evidence described in the scientific literature to date. The iSS-related hearing loss is described as sensorineural of variable degree and symmetry. The vestibular dysfunction appears to be of mixed central and peripheral vestibular origin. The AViSS study, despite demonstrating the heterogeneity in the auditory and vestibular deficits in individuals with iSS, allows to identify the origin of the audiovestibular dysfunction – based on the clinical test results – along the audiovestibular pathway. It appears to originate beyond the receptor (end-) organs in the majority of cases, with a novel finding of central auditory deficits suggestive of the auditory cortex involvement. Central vestibular

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findings other than cerebellar involvement may also be present in individuals with iSS however this may need to be evaluated in dedicated studies.

The findings of central auditory dysfunction are corroborated by the results from the study in Chapter 6 which suggest central auditory involvement in individuals with iSS as identified using hearing-specific PROMs.

Through this work it was possible to identify a high prevalence of the olfactory dysfunction (AViSS study, Chapter 3) and the presence of an association between the hearing thresholds and olfactory test scores. This suggests that the olfactory dysfunction may be highly prevalent in individuals with iSS. These findings also suggest that the pathophysiological processes affecting CNI and CNVIII might be synchronous.

The heterogeneity of the audiovestibular findings identified in the AViSS study may be explained by the presence of the likely secondary causes for hearing loss and imbalance in several study participants but may also represent various disease stages of the participants, although no formal grading system for iSS severity exists to date. The findings of normal auditory and vestibular function several cases suggests that the radiological findings (necessary for the diagnosis of iSS) may precede the clinical stage of the disease or perhaps iSS may have been halted in these individuals due to spontaneous self-resolution of the bleeding.

While the attempts have been made by several research groups to quantify the radiological appearance of haemosiderin deposits, and haemosiderin distribution in iSS has been described to date, there have been no dedicated studies to describe the pattern of haemosiderin distribution in individuals with iSS and quantify their

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radiological appearances in a systematic manner with a simple yet robust tool. The second research study (QUASARS, presented in Chapter 4 of this work) addresses this knowledge gap. It introduces an imaging rating scale which has been developed as a means to quantify haemosiderin deposits visualised on MRI and to report the frequency of the involvement of various anatomical structures of the CNS.

The study's results confirm the invariable involvement of the cerebellar superior vermis and folia, and the common finding of the brainstem involvement which are likely to explain the findings of central vestibular dysfunction observed in the majority of cases in the AViSS study, although as previously stated, central vestibular dysfunction other than relating to cerebellar or brainstem involvement may also exist and needs to be assessed in a dedicated study.

Furthermore, the rating scale scores and the involvement of the CNVIII and Sylvian fissures appear to correlate with the auditory function in individuals with iSS. Another key significant finding of the QUASARS study is that the rating scale has excellent level of inter- and intra-rater agreement. It is simple to use and does not require any additional software or dedicated training. It can be used by the clinicians or researchers who are knowledgeable of the relevant anatomy of the CNS and who are also familiar with the radiological appearances of haemosiderin on MRI and are able to recognise the pattern of haemosiderin distribution along the surfaces of the key anatomical structures involved in iSS.

While the rating scale appears to have excellent reliability to quantify haemosiderin burden and the scores appear to correlate with the objective measures of hearing loss in individuals with iSS, it cannot assess the impact of the functional and symptom burden of iSS on the individuals' HRQoL. This is assessed in the last

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research study (QoL in iSS and ARHL, Chapter 6 of this work). It is the first study to date to evaluate HRQoL in individuals with iSS, demonstrating that the overall health-state scores in individuals with iSS may be on the par with the scores identified in populations with other complex neurological disorders (74). The study also demonstrates that the HRQoL in iSS is impacted in several domains, of which the hearing domain appears to be worst affected, followed by such domains as mobility and pain.

The uniform focus of this work is on the population with the diagnosis of iSS. The significance of the findings from the studies included in this work should be viewed in the context of our current knowledge on iSS and regarding other rare complex neurological and neuro-otological conditions. It may be that the body of knowledge as well as clinicians' awareness regarding such conditions as FRDA, SCA, CANVAS is greater than that of iSS. Historically, the clinical knowledge about iSS and the research opportunities have been limited. The prevalence of iSS has not been studied in the UK population to date. This knowledge gap is addressed in the third research study of this work which is described in Chapter 5 (UKB iSS prevalence study). This study is the first of its kind to estimate iSS prevalence in a UK population sample, and its findings confirm the iSS status of a rare disease as defined by the European Parliament. This study findings appear to be consistent with the prevalence of iSS reported by other research groups in non-UK general and hospital populations. Another significant finding of this study is that the iSS prevalence appears to be comparable to the prevalence of other complex neuro-otological disorders described above. The study thus highlights the unmet need for further research into iSS and the need to increase clinicians' awareness of this disorder.

The clinical implications of this work are several. The detailed description of the iSS-related audiovestibular phenotype provides the clinicians with the information regarding the possible findings in individuals with iSS when assessing their hearing and balance function. It sets forth the example of which tests are needed for a comprehensive evaluation of auditory and vestibular function in such patients and highlights the role of the PROMs which should be considered alongside the objective clinical measures. The knowledge regarding the audiovestibular phenotype will also be helpful for informing a dedicated management plan for auditory and vestibular rehabilitation in this population.

This work also highlights the need for clinicians to include iSS in the differential diagnosis when evaluating patients with auditory or vestibular dysfunction or both, particularly when the hearing loss is more marked than expected for the patient's age group, and if there is history of previous CNS trauma or surgery or history suggestive of an episode of spontaneous CSF leak with low CSF volume state prior to iSS.

It is plausible that the iSS-related radiological features in the absence of audiovestibular dysfunction may signify early or pre-clinical stage of the disease as several patients in our cohort were identified with the radiological findings of iSS and in whom the audiovestibular function was normal or minimally abnormal. Timely assessment of such patients and patients in whom iSS may be suspected would allow for early treatment initiation such as attempt to repair the likely causative lesion or initiation of iron-chelating agent. This may halt the bleeding into the CSF and possibly disease progression and associated functional decline, although there is minimal clinical evidence to support this (14). Early rehabilitative auditory and

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vestibular measures may allow to maintain adequate functional levels and maintain or improve HRQoL in the affected individuals.

QUASARS can be considered by the clinicians during the initial diagnosis of patients with iSS patients – to confirm the haemosiderin distribution on MRI is consistent with the radiological diagnostic criteria for classical iSS and rule out other types of siderosis. The findings regarding the prevalence of iSS in a UK sample highlight the need for resource allocations for clinical and research activities and to increase the clinicians' awareness of iSS as it is likely to be encountered in the clinical setting on the par with other rare neuro-otological disorders, as mentioned earlier.

The overall limitations of this work include its in-part retrospective nature, the cross-sectional design and lack of control groups for most of the research studies, and relatively small sample sizes. The results of the AViSS and QUASARS studies should be interpreted with caution for cases in which there is a gap of 12 months or more between auditory or vestibular assessments or the imaging as the results may be due to disease progression. The work includes minimal information on natural history of iSS and does not explore the longitudinal analysis of the findings. The findings cannot be viewed in the context of the treatment status of the individuals with iSS nor does this work address the current lack of iSS severity grading.

The rarity of iSS can limit research opportunities, particularly regarding a sample size of the study as most studies to date include cohorts in single or teen figures. To overcome this limitation a careful consideration should be given to the study design such as including multiple research (or recruitment) sites or undertaking a study of longer duration with a wider window for recruitment. Longitudinal studies are needed that would allow to monitor the audiovestibular function at the earliest possible

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clinical stages of this condition or in the pre-clinical stages in cases with normal

audiovestibular function yet radiological findings suggestive of iSS, to determine their

change, including the radiological changes, over time – whether such findings may

be consistent with disease progression or with the response to treatment, and

whether these clinical and imaging markers can be used to reliably monitor clinical

changes over time.

General population studies with a large sample size are needed to more accurately

estimate the prevalence of iSS, facilitated using automated imaging analysis.

Longitudinal studies that explore susceptibility factors and pre-clinical stage of iSS

are needed to better understand the natural history of this disease and identify the

role of screening and long-term follow-up of the susceptible individuals, as well as

the role of early diagnosis and treatment in the pre-clinical stage of the disease.

Future research studies should include the PROMs to assess the scores against the

objective clinical measures including determining if an association exists between

the HRQoL scores and clinical measures, as well as hearing- and dizziness-specific

PROMs and the respective clinical findings in the individuals with this condition, thus

determining these instruments' face validity in the iSS population.

7.1 Overall conclusion

In summary, this project has allowed to expand the current knowledge on iSS and to

close several knowledge gaps which include: detailed phenotyping of the

audiovestibular function in iSS, determining the auditory profile using PROMs, and

identifying the most likely site of lesion along the audiovestibular pathway;

determining the role of imaging as a marker which could be used to assess for

disease burden alongside the objective clinical measures; establishing the

prevalence of iSS in a general UK population sample and in the context of other rare

neuro-otological disorders, and determining the impact of iSS on the HRQoL. Future

studies and, where feasible, of longitudinal design, need to focus on the natural

history of the disease, attempt to introduce disease severity grading system and

focus on developing new treatment modalities, and determining the treatment safety

and efficiency profiles of the currently available treatment options through controlled

trials, whether randomised or not.

APPENDICES

Appendix 1

Institutional normative data Normative data for auditory brainstem responses, electro-(video-)nystagmography, caloric irrigation and vestibular evoked myogenic potentials.

<u>Normative data for auditory brainstem responses</u>

Synergy (90 dB nHL)

Wave	I	III	V	I-III	III-V	I-V	IAD V	IAD I-V
Latency (msec)	1.31 - 1.83	3.40 - 4.08	5.16 - 6.01	1.83 - 2.52	1.49 - 2.19	3.54 - 4.48	<0.22	<0.38

Sierra Wave AEP (80 dB nHL)

Wave	I	III	V	I-III	III-V	I-V	IIIc	IVc	Vc
Latency (msec)	< 1.89	<4.01	<5.93	<2.32	<2.12	<4.24	<3.96	<5.12	<6

<u>Normative data for computerized ENG analysis</u>

Gaze (0°, 30°)*

	With fixation	Without fixation
SPV (°/sec)	< 0.8	< 2.7

Legend: *Sample size n=44 (20 -82 yrs); SPV slow phase velocity.

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Velocity steps test (60°/sec)*

	SPV (°/sec)	GAIN	TIME CONSTANT (Sec)	DP-SPV (%)	DP-TC (%)
Range	12.4 – 48.1	0.2 – 0.8	3.6 – 22.8	< 15.8	< 25.5
Mean	30.24	0.50	13.20	5.94	10.55
SD	8.91	0.15	4.82	4.95	7.46

Legend: *Sample size n=44 (20 -82 yrs); DP directional preponderance; SPV slow phase velocity; TC time constant.

Sinusoidal harmonic acceleration test (0.2 Hz, 40°/sec)*

	SPV (°/sec)	GAIN	DP (%)
Without Fixation	4.2 - 23.7	0.11 – 0.59	< 20.0
With Fixation	< 4.0	< 0.10	

Legend: *Sample size n=44 (20 -82 yrs); DP directional preponderance; SPV slow phase velocity.

Optokinetic nystagmus (40°/sec)*

SPV (°/sec)	GAIN	DP (%)
26.1 – 44.9	0.65 – 1.13	< 11.9

Legend: *Sample size n=44 (20 -82 yrs); DP directional preponderance; SPV slow phase velocity.

Smooth pursuit*

	SPV (°/sec)	GAIN	DP (%)
0.1 Hz	15.0 – 21.9	0.80 – 1.16	< 8.4
0.2 Hz	24.0 – 41.9	0.63 – 1.11	< 11.5
0.3 Hz	26.4 – 62.2	0.46 – 1.10	< 9.7
0.4 Hz	29.6 – 76.6	0.38 – 1.02	< 17.7

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Legend: *Sample size n=44 (20 -82 yrs); DP directional preponderance; SPV slow phase velocity.

Normative data for VNG analysis

- Departmental norms: 20-25% is borderline CP and DP, >25% is significant.

- Manufacturer's normative data were used for other VNG tests (276).

- Vertical Nystagmus: ≥6˚ is significant.

Normative data for oVEMP 500 Hz bone-conducted*

N10 msec	P15 msec	Asymmetry Ratio %
10.2 - 12.3 Mean: 11.61 SD: 0.64	14.0 – 17.3 Mean: 15.66 SD: 0.84	Significant if >34%

*Data collected from 40 normal subjects aged 18-65 years with normal auditory and vestibular function. Legend: msec milliseconds; SD standard deviation.

Normative data for oVEMP 500 Hz air-conducted

N10 (msec)	P17 (msec)	Asymmetry Ratio %
10.2 - 12.3	15.0 – 20	Significant if >37%

Thresholds below 80 dB nHL (normalised hearing levels) are abnormal.

Normative data for cVEMP 500 Hz air-conducted*

Threshold (dB SPL)	Threshold asymmetry (dB)	Amplitude asymmetry (%)	P13 (msec)	N23 (msec)	P13 inter-aural diff limit (msec)	N23 inter-aural diff limit (msec)
100-125	10	38.0	13 -20	20 – 30	2.7	4.0

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*Data collected from 40 normal subjects aged 20-60 years with normal auditory and vestibular function. Legend: diff difference; dB decibel; SPL sound pressure level; msec milliseconds. EMG cVEMP (min-max): 20 µV to 100 µV, where rectification is applied.

Normative data for caloric test

CP: ≤20%; DP ≤25% directional preponderance. For direct observational test: CP within 8% and DP within 12%.

Normative data for vHIT

Manufacturer's normative data were used:

VOR gain value range 0.8-1.20 for lateral impulse; 0.7-1.20 for RALP/LARP impulse (259).

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Appendix 2 QoL in iSS and ARHL study-related documents

STUDY SPECIFIC QUESTIONS

Q1. Please state **your age**

Q2. Please state y**our country of residence** _____

Q3. Are you (tick as appropriate)**:**

        Male [ ]   Female [.]

Q4. Have you been diagnosed with (tick as appropriate):

        superficial siderosis [.]

        age-related hearing loss [.]

Q5. How old were you when the above diagnosis was made? _____

Q6. Do you currently have problems with your hearing?

    Yes [.]

    No [.] (Please proceed to Question 15)

Q7. Do you find difficulty hearing in the presence of background noise?

    Yes [.]

    No [.]

    Sometimes [.]

Q8. How old were you when you first noticed hearing problems? _____

Q9. What is your current hearing level as advised by your health-care professional (if known)

        Not sure [.]

        Right ear: normal[ ] mild[.] moderate[.] severe[.] profound [.]

        Left ear: normal[ ] mild[.] moderate[.] severe[.] profound [.]

Q10. Do you currently have any devices to help with your hearing? (Please tick all that apply)

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None [.] (please proceed to Question 15)

Right hearing aid [.]

Left hearing aid [.]

Right cochlear implant [.]

Left cochlear implant [.]

CROSS device [.]

Assistive device for work/school [.]

Other device [.]

Q11. Please state how old were you when the hearing device was fitted?

For right ear _____

For left ear _____

Not applicable [.]

Q12. Have you found the hearing device helpful?

Yes [.]

Somewhat [.]

No [.]

Q13. Without the hearing device, can you hear any sound at all?

No [.]

Yes right ear [.]

Yes left ear [.]

Some in each ear [.]

Not applicable [.]

Q14. How much do you use your hearing device on a weekly basis?

Daily [.]

Most days [.]

Every other day [.]

Once per week or less[.]

Never [.]

Not applicable [..]

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Q15. Do you get noises (tinnitus) in your ears?

No [.]

Yes both ears [.]

Yes right ear [.]

Yes left ear [.]

Q16. Is the tinnitus:

Right ear: not bothersome [.]   bothersome[.]   distressing [ ]

Left ear: not bothersome [.]   bothersome[.]   distressing [ ]

Not applicable [ ]

Q17. Do you suffer from discharge (fluid) from your ears?

No [.]

Yes both ears [.]

Yes: right ear [.]

Yes left ear [.]

Q18. Have you ever had a perforation of your eardrum?

No [.]

Yes, right ear drum [.]

Yes, left ear drum [.]

Q19. Have you ever had surgery on your ears?

No [.]

Yes but not sure what exactly was done [.]

Yes, right ear [.]:

eardrum[.] mastoid[.] middle ear bones[.] balance organ[.]
other[.]

Yes, left ear [.]

eardrum[.] mastoid[.] middle ear bones[.] balance organ[.]
other[.]

Q20. Does anyone in your family have hearing problems, other than related to age?

Yes [.]

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No [ ]

Q21. For siderosis participants:

Do you know what was the likely event that caused siderosis?

Yes [.]. No [.]

Q21. How old were you when the likely causative event took place? _____

Q22. Are you or have you received any treatment for siderosis?

No [.]

Yes, surgery [ ] Please state the year of surgery _____

Yes, medication [.] Please state the year medication was commenced _____

please state the year medication was stopped _____

Please tick if treatment is ongoing [.]

Q23. Is English your first language?

Yes [.]

No [.]

END OF STUDY-SPECIFIC QUESTIONS

Quality of Life in iSS and ARHL: Online Survey
UCL REC 17413/001 Consent Form v 1.1 01-MAR-2020

FULL TITLE OF THE STUDY
Impact of hearing disability on overall quality of life in (infratentorial) superficial siderosis versus in age-related hearing loss
(Student Study)

SHORT TITLE
Quality of Life in iSS and ARHL: Online Survey

Consent questions (after introduction and before actual survey):
"In order to proceed with the survey, please agree with the below statements by clicking on the box next to each statement.

1. *I confirm that I have read the study participant information sheet (version 1.0).* ☐

2. *I confirm that I am at least 18 years of age and that I have been diagnosed with either*

    - *superficial siderosis (infratentorial) of the central nervous system* ☐

        or

    - *Age related hearing loss* ☐

3. *I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.* ☐

4. *I understand that my confidentiality will be respected subject to legal constraints and professional guidelines, and that despite the data being collected anonymously, confidentiality may not be guaranteed due to the limited size of the participant sample.* ☐

5. *I understand that relevant sections of my online anonymised responses collected during the study, may be looked at by individuals from UCL Ear Institute, UCL Institute of Neurology, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my online responses.* ☐

6. *I consent for the anonymised information collected about me online to be used to support other research in the future, and for it to be shared anonymously with other researchers.* ☐

7. *I consent to take part in the study* ☐

Study Consent Form

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Participant Information Sheet

UCL Research Ethics Committee Approval ID Number: 17413/001

Title of Study:

Impact of hearing disability on overall quality of life in (infratentorial) superficial siderosis versus in age-related hearing loss

(Student Study)

Short Title of Study:

Quality of life in (infratentorial) superficial siderosis and in age-related hearing loss

Department:

Department of Neuro-otology, Faculty of Brain Sciences, Ear Institute, University College London

Name and Contact Details of the Study Co-ordinators:
1. Natallia Kharytaniuk
2. Amir Ala Mazaheri

Name and Contact Details of the Chief Investigator:

Professor Doris-Eva Bamiou

1. Invitation

You are being invited to participate in this student research project ("the study"). We thank you for reading this information. Before you decide whether to take part, it is important that you understand the nature of this study, what your participation in it will mean for you and what its results may bring to you and to science. it is important that you read the following information carefully and discuss it with others if you wish. We will be happy to answer your questions or provide you with more information.

2. What is the project's purpose?

This study is designed to assess the impact of hearing problems on the quality of life of individuals with (infratentorial) superficial siderosis (which is a very rare neurological condition) and in those with age related hearing loss.

Infratentorial superficial siderosis (also known as superficial siderosis of the central nervous system) is characterised by a trickle of blood through a defect in the sheath that covers the brain or spinal cord. When blood is broken down, iron gradually becomes deposited on the surface of the brain, brain-related structures and/or spinal

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cord. Most often, hearing is involved. Because it is very rare and can cause significant hearing loss we would like to gain more information about the impact of this disease on quality of life and how hearing problems impact the quality of life in individuals with this diagnosis. We would like to compare the results from participants with this condition with the results from the participants with age-related hearing loss.

This is an online survey which contains commonly used general quality-of-life and hearing-specific questionnaires. This will be done in anonymised format as a once-off measure. The results of this study will help us understand how hearing problems may impact the quality of life in both groups and how they differ between the two groups. This may in turn may be valuable in the clinical setting in the future when assessing so the values can be compared to those obtained in this study, at the time of diagnosis of either (infratentorial) superficial siderosis or age-related hearing loss. These in turn may be useful in monitoring progression of symptoms or response to treatment or to rehabilitative measures.

3. **Who are we looking for?**
We would like to invite individuals who are:

- at least 18 years of age
   AND
who have a known/CONFIRMED diagnosis of either:

-Superficial siderosis (infratentorial), also known as superficial siderosis of the central nervous system

   OR

-Age-related hearing loss

4. **Do I have to take part?**

Taking part in this study is entirely voluntary. If you volunteer to participate in this study you can withdraw at any time without giving a reason and without it affecting you in any way. Anonymised data collected before you decide to withdraw from the study might still be used for analysis. A decision to withdraw from the study or a decision not to participate in this study will not disadvantage you in any way.

5. **What will happen to me if I take part?**

If you decide to participate in this study, we will ask to indicate your consent as described below. This will be done in an online format, and you will not be able to proceed to the study questions without your consent and confirming that you understand the purpose and nature of this study, that you are at least 18 years of age, and that you have previously received a formal diagnosis of either (infratentorial) superficial siderosis or age-related hearing loss.

Your participation in this study will be anonymous and will entail completing the online questionnaires that describe your quality of life overall and with regards to your hearing. We would also like to ask your gender, your current age, when (the

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age at which) you were diagnosed with superficial siderosis or age-related hearing loss (you must indicate which of the two is applicable) and whether you have received or are receiving any treatment (surgery or medication or any hearing device or intervention). We would also like to know your current level of hearing. There are six questionnaires in total which may take between 5 and 10 minutes each to complete (between 30-60 minutes in total). We would like to ask you to set aside some time when completing the questionnaires. You would only need to complete the set of questionnaires once.

We rely on you to provide us with as accurate information as possible and to complete the questionnaires to the best of your ability – this would help us maintain the integrity and high quality of this research.

6. What are the possible disadvantages and risks of taking part?

Your involvement is limited to answering a set of questionnaires which are commonly used in clinical and research settings and are unlikely to cause any upset. If you have a concern about any aspect of this study, you may decide not to complete the questionnaires or any part thereof or omit any question that you find upsetting or disturbing. You can also discuss this by contacting the study research team (the study co-ordinators or the Chief Investigator, as above).

7. What are the possible benefits of taking part?

There are no immediate benefits from participating in this research project. You will not be paid or reimbursed for your participation in this study.

8. What if something goes wrong?

In case you have a concern about any aspect of the study, please do not hesitate to contact the study co-ordinators. In case there is any complaint please contact the Chief Investigator Professor Doris-Eva Bamiou. However, the participants should also be informed that should they feel their complaint has not been handled to their satisfaction (e.g. by the study research team) that they can contact the Chair of the UCL Research Ethics Committee – *ethics@ucl.ac.uk*

9. Will my taking part in this project be kept confidential?

All data will be collected in anonymous format and stored in accordance with the General Data Protection Regulations (GDPR) and Data Protection Act (DPA) 2018. Your participation will not be identified in any ensuing reports or publications.

10. Limits to confidentiality

Please note that confidentiality will be respected subject to legal constraints and professional guidelines, and that despite the data being collected anonymously, confidentiality may not be guaranteed due to the limited size of the participant sample.

11. What will happen to the results of the research project?

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The results of this study will retain no personal information so participants cannot be identified in any published articles. The results will be published in scientific journals and public platforms, and as part of students' Masters and PhD Thesises. You can obtain the results and findings of this study by contacting the study co-ordinators.

12. Local Data Protection Privacy Notice

Although no personal data will be collected or stored as part of this study, the controller for this study will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at

data-protection@ucl.ac.uk

This 'local' privacy notice sets out the information that applies to this particular study. Further information on how UCL uses participant information can be found in our 'general' privacy notice: For participants in research studies, click here

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices. The data collected as part of this project will be in anonymised format. No personal data will be collected. If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk.

13. Who is organising and funding the research?

This study is sponsored and organised by University College London (UCL). It is supported and part-funded by: (1) the National Institute for Health and Research (NIHR) University College London Hospitals Biomedical Research Centre (BRC) Deafness and Hearing Problems Theme; (2) the Bernice Bibby Research Trust (UK Registered Charity No 1058703). Additional funding for Health Utilities Index (Mark3) license use was sought and granted by (3) Health Utilities Index Inc.

16. Contacts for further information

Dr Natallia Kharytaniuk (PhD Student/Study Co-ordinator)

Mr Amir Ala Mazaheri (MSc Student/Study Co-ordinator)

Professor Doris-Eva Bamiou (Supervisor/Chief Investigator)

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