Hearing impairment after subarachnoid haemorrhage

Running head: Hearing loss after SAH

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Abstract

Background. Subarachnoid haemorrhage (SAH) survivors experience significant neurological disability, some of which is under-recognized by neurovascular clinical teams. We set out to objectively determine the occurrence of hearing impairment after SAH, characterize its peripheral and/or central origin, and investigate likely pathological correlates.

Methods. In a case-control study (n=41), participants were asked about new onset hearing difficulty three months post-SAH, compared with pre-SAH. Formal audiological assessment included otoscopy, pure tone audiometry, a questionnaire identifying symptoms of peripheral hearing loss and/or auditory processing disorder, and a test of speech understanding in noise. A separate cohort (n=21) underwent quantitative susceptibility mapping (QSM) of the auditory cortex six months after SAH, for correlation with hearing difficulty.

Results. 23% of SAH patients reported hearing difficulty that was new in onset post-SAH. SAH patients had poorer pure tone thresholds compared to controls. The proportion of patients with peripheral hearing loss as defined by the World Health Organization and British Audiological Society was however not increased, compared to controls. All SAH patients experienced symptoms of auditory processing disorder post-SAH, with speech-in-noise test scores significantly worse *versus* controls. Iron deposition in the auditory cortex was higher in patients reporting hearing difficulty *versus* those who did not.

Conclusion. This study firmly establishes hearing impairment as a frequent clinical feature after SAH. It primarily consists of an auditory processing disorder, mechanistically linked to iron deposition in the auditory cortex. Neurovascular teams should inquire about hearing, and refer SAH patients for audiological assessment and management.

Introduction

Subarachnoid haemorrhage (SAH) survivors experience significantly reduced quality of life which is not well reflected by conventional clinical outcome measures such as the modified Rankin Scale (mRS) or Glasgow Outcome Score (GOS). This "hidden" disability is the topic of increasing research and is probably multifactorial arising from cognitive deficits[1] and post-traumatic stress disorder[2]. Hearing impairment, whether it is of peripheral and/or central origin, may be another mediator of poor outcome. During development of a SAH-specific clinical outcome tool[3], which involved sessions with SAH patient focus groups, we noted a high prevalence (21.4%) of new onset subjective hearing difficulty post-SAH. In a retrospective analysis of prospectively collected data from 277 SAH patients, Vos *et al* investigated the prevalence and risk factors of subjective hearing difficulty after SAH[4], concluding that subjectively reported hearing difficulty occurs in 1 of every 5 SAH patients.

Hearing difficulty can be peripheral in nature (i.e. present as a decline in hearing acuity on an audiogram) or central (i.e. typically a normal pure tone audiogram but increased difficulty hearing in noise and processing speech). This latter category is known as auditory processing disorder (APD)[5]. While an audiogram provides information around the detection of pure tone (i.e. hearing sensitivity) it does not provide information about real world signals such as speech perception, particularly in less favourable listening environments. APD has its origins in impaired neural function, which includes both the afferent and efferent pathways of the central auditory nervous system (CANS), as well as other neural processing systems that provide 'top down' modulation of the CANS[5]. These other systems include, but are not limited to the cognitive functions of language, speech, attention, executive function, memory and emotion. APD is often found alongside and may contribute to primary disorders of those systems, and may thus include both auditory and cognitive elements[5]. Individuals with APD typically present with listening difficulties and other behaviours consistent with hearing loss, despite a normal audiogram. These behaviours include greater difficulty hearing when there is background noise (the most common complaint), mishearing speech and frequent requests for repetition[5]. A number of pathologies such as early brain injury, vasospasm, vascular injury and iron deposition occurring after SAH have potential to affect peripheral and central auditory systems including the cochlea, vestibulocochlear nerves, brainstem nuclei and higher areas of the CANS.

The British Society of Audiology differentiates between three categories of APD[5]: (1) developmental APD (presenting in childhood); (2) acquired APD (associated with ageing or a known post-natal event, such as an infection or neurological trauma, e.g. SAH); and (3) secondary APD (where APD occurs in the presence, or as a result, of peripheral hearing loss).

We hypothesized that (i) hearing impairment occurs after SAH, more than one would expect in a control population of similar age and gender, (ii) hearing impairment after SAH is multifactorial, including peripheral hearing loss and central APD. To address these hypotheses, we performed a prospective study of SAH patients and controls, with detailed objective audiological assessment, in order to better understand and quantify the hearing difficulties reported by SAH patients.

Methods

Definitions

In this manuscript we use the term *hearing loss* to define diminished hearing on an audiogram, *APD* to define hearing difficulty of central origin, *hearing impairment* to define both hearing loss and APD, and *hearing difficulty* for the subjective report of decreased hearing by participants.

Cohort 1: audiological study

This was a prospective case-control study of hearing impairment after SAH, recruiting patients from a neurovascular specialist nurse follow up clinic for SAH patients treated by endovascular coiling (surgically clipped patients were followed up in a surgical clinic), three months post-ictus. Control participants were recruited by advertisement in the University and Hospital. For SAH and control participants, inclusion criteria were age greater than 18 years and English language proficiency, while exclusion criteria consisted of otological abnormalities, exposure to loud noise in previous 24 hours, and conductive hearing loss, as defined by an air bone gap > 12dB (two standard deviations from the normative data[6-8]). For SAH participants, an additional inclusion criterion was a post-ictal interval of at least three months after aneurysmal or non-aneurysmal atraumatic SAH. The study was conducted under National Research Ethics Committee Approval (LREC ref: 12/SC/0666, for SAH patients) and institutional approval (ERGO ref: 17752, for control participants).

For new onset hearing difficulty, patients were asked whether they noticed a change in hearing subsequent to the SAH. Formal audiological assessment included otoscopy, pure tone audiometry, a questionnaire identifying symptoms of peripheral hearing loss and/or APD and a speech-in-noise test.

Since there are currently no validated APD adult questionnaires[5], one was adapted from the Children's Auditory Performance Scale[9] for the purposes of this study, and consisted of 20 questions (Supplementary Table 1). The questionnaire took the participant's otological history and enquired about otological and hearing impairment, comparing before to after SAH. Specifically, it covered hearing in the presence of competing noise, hearing in a quiet environment, auditory memory sequencing, localization, difficulty using a telephone, mishearing of words and hyperacusis, pre and post SAH. The sum of responses to APD questions was converted to a percentage, and used as an ecological or real life report (i.e. subjective measure) of APD, before and after SAH.

Otoscopy (Heine Mini 3000) and PTA (Kamplex AD 27, TDH headphones, B27 bone transducer with Radioear P3333 headband) were carried out in accordance with British Society of Audiology (BSA) recommendations[10]. Hearing loss was defined according to BSA criteria[10] (mean threshold at 0.25, 0.5, 1, 2 and 4 kHz is >20dB in any ear) and World Health Organization (WHO) criteria[11] (mean threshold at 0.5, 1, 2 and 4 kHz is >25dB in better ear).

The fixed noise Bamford-Kowal-Bench (BKB) test was used as a speech-in-noise test[12]. It was administered using Sennheiser HAD 300 headphones and a laptop with BKB test material. The test was comprised of recorded sentences presented against a background of noise (multi-speaker babble) with a fixed level of -10dB signal-to-noise ratio. The intensity level of the recorded sentences was set at each participant's most comfortable level to accommodate for differences in peripheral hearing thresholds. To minimize interference from cognitive deficits, a pre-requisite was that participants were able to correctly repeat BKB sentences in quiet, i.e. the absence of competing noise. Each BKB sentence is scored based on correctly repeated keywords, culminating in the overall percentage score of correct answers.

SAH severity at presentation was assessed by the World Federation of Neurosurgical Societies (WFNS) grade[13], overall SAH bleed size was assessed by the modified Fisher scale[14], and disability at three months was assessed by the modified Rankin Scale[15] and Glasgow Outcome Score[16, 17]. Delayed ischaemic neurological deficit (DIND) was defined as

the occurrence of hemiparesis, dysphasia, a new focal deficit 72 hours post-SAH or a GCS drop of 2 or more not attributable to other causes[18]. Transcranial Doppler flow was measured through both middle cerebral arteries (MCA) at periodic intervals during admission; the maximal blood flow was recorded and a threshold of 200 cm/second was used to define severe vasospasm[19].

The extent of blood clot present in the Sylvian fissure on the admission computed tomography scan was scored visually (using a visual analogue score as follows: 0 for no blood clot, and 1, 2 and 3 for partial filling, complete filling and dilation of the Sylvian fissure with blood respectively) and measured by its maximum thickness in millimetres in the posterior limb (in cases where blood was present in both Sylvian fissures, the worst side was considered). The two variables were highly correlated (Spearman $r=0.86$, $p<10^{-11}$) and gave the same results in all analyses. The presence of blood around the vestibulocochlear nerves was recorded, as either present or absent, and whether symmetrical or asymmetrical, and in the case of the latter, which side had most blood clot.

Cohort 2: susceptibility-weighted imaging study

A separate group of 21 SAH patients who had previously been recruited to develop a new SAH specific outcome tool and map deficits against location of iron deposition underwent susceptibility-weighted magnetic resonance imaging (MRI) of the brain six months after ictus. These are not the same patients in Cohort 1. On the day of imaging they were asked whether they had experienced a change in their hearing after SAH, compared to before SAH, during completion of a SAH outcome tool[3]. They were also asked about their handedness to determine hemisphere dominance. Three-dimensional susceptibility-weighted image (SWI) datasets were acquired axially on a 1.5 Tesla Siemens Symphony MRI scanner (Siemens Healthcare AG, Erlangen, Germany) with radiofrequency spoiling and flow compensation in all three orthogonal gradient directions (TR=50ms, TE=40ms, flip angle = 12°, resolution=1.3 x 0.9 x 2.0 mm^3). In addition an isotropic three-dimensional structural T1-weighted image was acquired (TR = 2200ms, TE = 2.88ms, flip angle = 12°, resolution=1.2 x 1.2 x 1.2 mm). SWI images were processed using the software package SPIN (Signal Processing in NMR, SpinTech, Detroit, MI, USA) to generate susceptibility weighted imaging and mapping (SWIM) volumes for quantitative susceptibility mapping (QSM) (examples in Fig. 1). All subsequent image processing was performed in FMRIB Software Library (FSL)[20]. Structural T1 was brain extracted using BET[21]. Structural T1 and SWIM

volumes were registered to the Montreal Neurological Institute (MNI) standard space, using FMRIB's non-linear image registration tool[22]. A grey matter T1 mask was produced using FAST[23] and susceptibility was quantified in the grey matter of Heschl's gyrus, planum polare and planum temporale using the Harvard-Oxford cortical atlas[24]. *A priori*, a voxel was considered to have detectable iron signal if its susceptibility value was greater than two standard deviations above the signal in white matter as calculated using a series of 10 age and gender-matched control patients undergoing follow up of non-ruptured aneurysms or aneurysm screening, on the same scanner. Blood clot volume on the admission CT was quantified using MIPAV (Medical Image Processing, Imaging and Visualization) v7.2. The CT image signal intensity threshold was set between 50 and 80 Hounsfield units, and converted to a binary mask. Regions of interest representing blood clot were drawn manually on each slice, and summed into single three-dimensional volumes.

Statistical analysis

Statistical analysis was conducted in SPSS v23. Group comparisons were performed with Student's t test for parametric data (age and BKB score), Wilcoxon's test for paired non-parametric data (APD questionnaire scores) and Mann-Whitney's test for unpaired non-parametric data (QSM). Cross-tabulated data was analysed with the Fisher exact test (gender, hearing loss, lateralization of hearing loss and blood). Analysis of covariance (ANCOVA) was used to correct for the effect of age on BKB score and PTA thresholds. Linear regression was used to explore predictors of APD and BKB scores. Logistic regression was used to explore predictors of sensorineural hearing loss. To investigate the role of hearing loss as a mediator in the causation of APD, regression-based mediation analysis[25] was performed using the regression path analysis modelling tool PROCESS[26, 27], with age as covariate. Significance for the indirect effect was tested using bootstrapping (n=5,000) with 95% intervals. Effect size was calculated and reported as percent mediation. Alpha was 0.05.

Results

Patient characteristics of Cohorts 1 and 2

The demographics and clinical features for participants in Cohorts 1 and 2 are shown in Table 1. Cohort 1 consisted of 41 SAH patients and 19 control participants. One SAH patient with conductive hearing loss was excluded, and one SAH patient withdrew half-way through the

assessment, resulting in 39 SAH patients and 19 controls meeting the inclusion criteria. Controls were similar in age and gender ($p > 0.05$, t-test and Fisher exact test respectively). Cohort 2 consisted of 21 SAH patients.

Cohort 1: auditory processing disorder

Patients were assessed at three months post-SAH. 23% of SAH patients reported a new hearing difficulty after SAH, compared to before SAH. When asked specifically about symptoms suggestive of APD, using the questionnaire, all SAH patients reported a change, comparing before SAH with three months after SAH. Wilcoxon paired testing revealed a significant difference between the APD questionnaire scores before and after SAH ($p=0.0002$, Fig 2, median scores were 94 before SAH (IQR 12) and 81 after SAH (IQR 25), out of 100). BKB testing revealed a significant difference in BKB scores between patients and controls ($p=0.007$, Fig 3, means of percentage correct were 61% ± 10% and 34% ± 19%), which was retained in an ANCOVA after correction for age. To see which factors predicted APD after SAH as measured by the BKB test, stepwise linear regression were conducted including age, gender, WFNS, Fisher, aneurysmal status, aneurysmal Rx, and Sylvian blood clot thickness. Only age was a significant predictor of the BKB score ($r^2=0.38$, beta=-0.62, $p<0.001$). The addition of DIND (available in 30 patients) or vasospasm (as maximal MCA blood flow or as a binary variable, available in 31 patients) did not affect the findings. There was no significant difference in Sylvian blood clot thickness between patients who experienced new onset hearing difficulty *versus* those who did not ($p=0.84$, t-test).

Both right and left PTA mean thresholds were poorer in patients *versus* controls, correcting for age (7.6 decibels increase in right PTA, $p=0.024$; 10.3 decibels increase in left PTA, $p=0.003$; ANCOVA; Fig 4). To see which factors predicted PTA mean threshold after SAH, stepwise linear regression were conducted including age, gender, WFNS, Fisher, aneurysmal status, aneurysmal Rx, and blood clot around the vestibulocochlear nerve: only age was a significant predictor of mean PTA threshold ($r^2=0.33$, beta=0.57, $p<0.001$). The addition of DIND (available in 30 patients) or vasospasm (as maximal MCA blood flow or as a binary variable, available in 31 patients) did not affect the findings.

APD may be acquired (associated with a known post-natal event, such as an infection or neurological trauma, e.g. SAH) or secondary (occurring in the presence, or as a result, of peripheral hearing loss). Since both APD and peripheral deficits were noted after SAH (Fig 2-4), we next assessed whether mean PTA threshold was contributing to APD. Mediation

analysis is a mathematical technique to assess whether a predictor (in this case SAH) affects a dependent variable (in this case APD as assessed by BKB score, assuming this variable represents APD severity) indirectly through an intervening variable, or mediator (in this case mean PTA threshold). Age was included as a covariate in view of its effect on both BKB and mean PTA threshold. The total and direct effects of SAH on BKB were highly significant (Fig 5). Mean PTA threshold had a minor, narrowly significant, effect on BKB, accounting for 11% of the total effect of SAH on BKB.

Cohort 2: iron deposition in the auditory cortex

Iron is deposited in the outer layers of the cortex after SAH[28, 29]. In a separate cohort of 21 SAH patients, SWI was performed six months after ictus; patients were asked whether they had experienced a change in their hearing after SAH, compared to before the SAH as part of their assessment with the recently-described SAH outcome tool[3]. The QSM results from SWIM were used to derive a relative measure of iron deposition in the auditory cortex, in patients with and without hearing difficulty, as shown in Fig 6A to C. All SAH patients had detectable iron signal in the auditory cortex, but this was more striking in those who experienced hearing difficulty (Fig 6G to I) *versus* those who did not (Fig 6D to F). In the non-dominant hemisphere, iron content in the auditory cortex was higher in patients with hearing difficulty (Fig 7A). This difference was more significant in the secondary auditory cortex (planum polare and planum temporale) than in the primary auditory cortex (Heschl's gyrus). There were no differences in auditory cortex iron content in the dominant hemisphere (Fig 7B).

Discussion

This controlled prospective study with objective audiological assessment firmly establishes hearing impairment, and more specifically APD, as a common clinical feature after SAH. Subjective evidence is reported by 20-25% of patients if simply asked about a new onset worsening in hearing with the SAH. Although around 25% of 40-70 year old people in the general population (UK Biobank study) report hearing difficulty[30], it is important to note that both in this study and the preceding one[4], the hearing difficulty reported by 20-25% was new onset in nature, i.e. presented only after SAH. If questioned specifically about symptoms in keeping with APD, all patients in this study reported the onset of such symptoms after their

SAH. Given the high prevalence of new hearing difficulty after SAH, affecting 20-25% of SAH patients, it is surprising how this clinical feature has so far been overlooked. The most likely explanation is that since SAH patients suffer from a multitude of neurological, cognitive and psychosocial deficits, hearing impairment has received less attention. There are currently also no validated APD adult questionnaires[5] which makes it difficult for the clinician to quantify and make decisions around onward referral and management. It is possible that hearing impairment contributes to the impact of SAH on patients' daily functioning, since hearing deficit affects quality of life[31]. In addition there is a reciprocal relationship between hearing difficulty and cognitive performance[32], which may amplify the impact of both. Further studies are needed to assess the impact of this common symptom on quality of life after SAH, and the relationship with cognitive decline. APD may include both auditory and cognitive elements[5]. The high co-occurrence of APD with language, attention, memory, and executive difficulties underscores the importance of a multi-faceted approach[5].

One cannot rely only on subjective questioning about hearing impairment since this may be influenced by recall and other subjective factors. Objective testing revealed marked evidence of hearing impairment after SAH, compared to a control group of similar age and gender. Hearing impairment may be either peripheral or central in origin. There was no difference in hearing loss as defined by BSA or WHO thresholds between patients and controls, but mean PTA thresholds were significantly poorer in SAH patients *versus* controls (i.e. lower responses to quieter sound levels). All participants reported new onset symptoms of APD post-SAH when questioned, and this was objectively confirmed in 59% of patients, who had BKB scores below the reference range. Mean PTA threshold had a minor, narrowly significant, effect on APD, accounting for 11% of the total effect of SAH on APD.

Auditory processing deficit: mechanisms

The underlying pathological mechanism underlying the occurrence of APD post-SAH is probably multifactorial, possibly including hypoxia, mechanical stretching, bystander damage from inflammation and neurotoxicity from extracellular haemoglobin and iron deposition. In this study hearing difficulty was associated with iron deposition in the auditory cortex. This is keeping with the previous finding that hearing difficulty was more likely to be associated with aneurysms of the middle cerebral artery, which supplies the superior aspect of the temporal lobe[4]. The location of the auditory cortex in the Sylvian fissure could potentially

increase susceptibility to pathology resulting from trapping of blood clot, haemoglobin and inflammatory cells in the fissure.

The side with maximum blood clot on the admission CT corresponded to the side with maximum iron deposition six months later (Supplementary Table 2). While thickness of blood clot in the Sylvian fissure on the admission CT did not correlate with objective hearing impairment three months after SAH, iron content in the auditory cortex six months post-SAH correlated with hearing difficulty. It is important to note that these two observations were made in two different study populations. There may be a threshold of blood clot volume above which iron deposition is seen. Also, one may speculate that the volume of blood clot and local deposition of iron within this region are not tightly linked, and factors other than the volume of Sylvian blood clot play a more important role in determining iron deposition in the auditory cortex six months later. Such factors may include the way blood settles after SAH, local cerebrospinal fluid dynamics, efficiency of clot resolution, and host inflammatory response.

Iron deposition in the non-dominant auditory cortex was associated with hearing difficulty, while iron deposition in the dominant auditory cortex was not. The most likely explanation for this is the fact that in patients with hearing difficulty, the blood clot was randomly more deposited on the non-dominant side, and the same was found for iron deposition (Supplementary Table 2). Another potential, but unlikely, explanation is that there are differences between right and left auditory cortices with respect to susceptibility to blood clot or iron deposition and associated neurotoxicity. Heschl's gyrus is smaller on the non-dominant side[33] and this may theoretically provide easier access to blood during SAH, though the difference is likely to be minor and non-consequential. It is also highly unlikely that the non-dominant auditory cortex impacts on auditory function after SAH at the exclusion of the dominant side. Both auditory cortices contribute to the perception of sound. Magnetoencephalography suggests that speech is not predominantly processed in the left hemisphere as traditionally thought, but instead engages cortical areas bilaterally with marked right hemispheric involvement[34]. There is multiple evidence supporting the concept of asymmetric speech parsing between the two cortices, such that different components of speech are analyzed in parallel, similar to a dual-core processor on a computer[35]. There appear to be two main specializations, which are linked. Firstly, the left auditory cortex responds better to rapidly modulated speech content, while right temporal cortex responds better to slowly modulated signals[36]. Plosive consonants need fast processing while fricative,

affricate, nasal, and liquid consonants, as well as vowels are longer in duration. Slowly modulation is important for discriminating syllables and in a wider sense appreciating different voices, prosody in speech and music. Secondly (and consequent to the first), the left auditory cortex has a higher temporal resolution, while the right auditory cortex is better at resolving spectral information since time is permitting[37]. Spectral information (pitch[37] and frequency modulation direction[38]), is another important determinant in perception of sound, with relevance to sentence type, prosody in speech and music.

Peripheral hearing deficit: mechanisms

The underlying pathological mechanism underlying the occurrence of the peripheral hearing deficit after SAH is also probably multifactorial. It is tempting to draw parallels with superficial siderosis[39], where chronic bleeding and iron deposition around the vestibulocochlear nerve results in a peripheral hearing problem. We did not find evidence for an association between blood clot around the eighth nerve and deficits in hearing thresholds, so it is likely that diffusion of blood products plays a more important role than apposition of blood clot. Other potential mechanisms include stretching of the vestibulocochlear nerve or damage to its nuclei and connections in the brainstem.

Implications for clinical management

It is important to ask about hearing difficulty after SAH in neurovascular follow-up clinics, and at the very least, symptomatic patients should be referred for audiological assessment. Peripheral hearing loss is an indication for hearing aid prescription, and is associated with a cost-effective improvement in quality of life[40, 41]. Assistive listening devices, designed specifically for people with normal hearing can also be used to treat APD, since critical speech elements are preserved and masking by background noise and reverberation are minimized. Long-term benefits of such systems have mostly been investigated in children[42-44], but have recently started to be applied in stroke[45, 46]. Current intervention strategies can be divided into three main categories, namely (1) modifying the listening environment (architectural interventions and acoustic treatments, i.e. adding soft furnishings, noise absorbent partitions/screens and assistive listening devices), (2) auditory training (computer and non-computer based) and (3) compensatory strategies (metacognitive and meta-linguistic strategies)[5]. Strategies modifying the listening environment have the highest evidence base[5]. A number of auditory training strategies may be used to treat symptoms of APD, though none

have been subjected to rigorous assessment in a randomized controlled setting[47]. Finally cognitive assessment of SAH patients in both research and clinical settings should be preceded by formal audiological testing, since over-diagnosis of cognitive dysfunction may occur in the presence of hearing difficulty[32].

Strengths and Limitations

This study has several strengths including the presence of a control group of similar age and gender, the use of objective measures of hearing difficulty, assessment of both peripheral and central components, and the availability of QSM measures of iron deposition. The study provides definitive evidence of hearing impairment after SAH and establishes that most of this is related to APD. It suggests that the pathological substrate is iron deposition in the secondary auditory cortex.

Limitations include the small sample size, the absence of clipped patients and the bias towards patients with better outcome. There is currently no validated APD questionnaire available for adults. The in-house questionnaire used for APD is not validated. APD may be overlap with cognitive deficits, which were not formally assessed; however we only proceeded to perform BKB testing if the participants could repeat the BKB sentences in quiet. APD may arise due to lesions at several points in the central auditory pathway, including the brainstem (cochlear nuclei, superior olivary complex, and inferior colliculus), the thalamus (medial geniculate nucleus)[48], the auditory cortex and its dorsal and ventral projection streams[49]. Brainstem-sensitive electrophysiological data (auditory brainstem responses and stapedial acoustic reflex thresholds) was not available. SWI artefact and resolution limits precluded detailed imaging study of the medial geniculate nucleus. Finally, tissue magnetic susceptibility may be related to other factors besides the quantity of iron in the tissue. Examples include an increase in the proportion of venous blood content and tissue oxygen extraction fraction (which would result in a higher concentration of paramagnetic deoxyhaemoglobin), changes in tissue microstructure which may alter the magnetic behaviour of iron-containing particles, and changes in diamagnetic calcium and myelin content[50]. Hence the linear relationship between QSM-derived and laboratory assays of iron in cadaveric brain[51] may break down in pathological conditions such as SAH.

Future directions

Hearing assessment and APD screen is recommended for patients post-SAH during follow-up. Reduced concentration and fatigue are common attributes post-SAH, and since many

SAH patients tend to have a low tolerance for lengthy assessments, further research is warranted to develop an optimal audiological test battery. Also needed is an evaluation of higher order functions, known to play a role in auditory processing. The high co-occurrence of APD with language, attention, memory, and executive difficulties[5] underscores the importance of an integrated and multi-faceted approach in assessing and managing the difficulties reported by SAH patient. Finally, a pragmatic randomized controlled trial of auditory screening and intervention after SAH is warranted.

Table 1. Participant characteristics. Mean and range[a], number and %[b], [c] t test, [d] Fisher exact test, NS = p>0.05. WFNS = World Federation of Neurosurgical Societies grade; mRS = modified Rankin Scale; GOSE = Glasgow outcome Score.

	STUDY 1			STUDY 2
	SAH	**Control**	***p***	**SAH**
Number	39	19		21
Age (years)[a]	59, 35-79	57, 26-76	NS[c]	57, 30-76
Modified Fisher grade[b]				
0	2, 5%			
1	7, 18%			
2	8, 21%			
3	9, 23%			9, 43%
4	13, 33%			12, 57%
WFNS grade[b]				
1	23, 59%			14, 67%
2	6, 15%			6, 29%
3	1, 3%			
4	6, 15%			1, 5%
5	3, 8%			
mRS at three months post-SAH[b]				
0	4, 10%			4, 19%
1	23, 59%			16, 76%
2	9, 23%			1, 5%
3	2, 5%			
4	1, 3%			
GOS at three months post SAH[b]				
3	1, 3%			5, 24%
4	5, 13%			6, 29%
5	33, 84%			10, 48%
Gender[b]				
male	13, 33%	6, 32%	NS[d]	3, 14%

female	26, 67%	13, 68%	18, 86%
Intervention[b]			
coiled	31, 79%		21, 100%
clipped	0, 0%		0, 0%
no aneurysm identified	8, 21%		
Aneurysm location[b]			
anterior	25, 64%		17, 81%
posterior	6, 15%		4, 19%
no aneurysm identified	8, 21%		

Figure legends

Figure 1: Susceptibility weighted imaging and mapping. A,E: magnitude images; B,F: filtered phase images; C,G: susceptibility-weighted images (SWI); D,H: quantitative susceptibility maps (QSM). A-D: SAH patient without new onset hearing difficulty. E-H: SAH patient with new onset hearing difficulty. Iron deposition can be observed in multiple locations as low signal intensity on the magnitude and filtered phase images and high signal intensity on the QSM image (such as within the red border, which encircles the Sylvian fissure and auditory cortex).

Figure 2. Hearing and auditory processing questionnaire. Lines connect APD questionnaire scores of individual patients before and after SAH. Wilcoxon test.

Figure 3. Speech-in-noise (Bamford-Kowal-Bench, BKB) test scores. The BKB score was the percentage of correct answers, Student t test.

Figure 4. Pure tone audiogram. ANCOVA estimated marginal means for right and left pure tone audiogram mean thresholds.

Figure 5. Regression-based mediation analysis: path diagram. A positive coefficient is indicative of poorer hearing when mean PTA threshold (peripheral hearing deficit) is the outcome, while a negative coefficient is indicative of poorer hearing when BKB score (APD) is the outcome. NS = $p > 0.05$, * = $p < 0.05$, **** = $p < 0.0001$

Figure 6: Auditory cortex region of interest (yellow in A-C). D-F: SAH patient without hearing loss. G-I: SAH patient with hearing loss. Red denotes voxels in the auditory cortex region of interest with detectable iron signal.

Figure 7. Quantitative susceptibility mapping. Medians (and interquartile range), Mann-Whitney test.

Supplemental File. Supplementary Table 1 (Otological/hearing history and auditory processing disorder (APD) questionnaire) and Supplementary Table 2 (Asymmetry of blood clot and iron deposition in the SAH population of the SWI study).

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Author contributions

N.C., C.V., L.F., D.B., and I.G. contributed to the conception and design of the study; all authors contributed to different aspects of data acquisition; S.M., O.M., L.D., H.T., R.S, and I.G. analysed the data; N.C. wrote the first draft of the manuscript; C.V., A.D., M.E.H., D.B, and I.G. contributed to the manuscript's revision; all authors approved the final version of the manuscript.

Conflict of interest

Nothing to report.

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