**Auditory outcome following aneurysmal subarachnoid haemorrhage**

Ben Gaastraa,b # (0000-0002-7517-6882)

Monica Ashokumarc

Diederik Bultersb (0000-0001-9884-9050)

Nicci Campbelld\* (0000-0001-6895-5434)

Ian Galeaa\* (0000-0002-1268-5102)

a: Faculty of Medicine, University of Southampton, Southampton, SO17 1BJ, UK

b: Department of Neurosurgery, Wessex Neurological Centre, University Hospital Southampton, Southampton, SO16 6YD, UK

c: Institute of Sound and Vibration Research, Faculty of Engineering and Physical Sciences, University of Southampton, United Kingdom

d: Auditory Implant Service, Faculty of Engineering and Physical Sciences, University of Southampton, Southampton, UK

\*Joint senior authors

#Corresponding author:

Email: bgaastra@nhs.net

Address: Faculty of Medicine, University of Southampton, Southampton, SO17 1BJ, UK

Telephone: 023 8077 7222

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Abstract (250 words)

Auditory deficits are increasingly recognised following aneurysmal subarachnoid haemorrhage (aSAH) and are thought to be of central rather than peripheral origin. Central hearing impairment, also known as auditory processing disorder (APD), often coexists with cognitive deficits and it is thought that APD has both auditory and cognitive elements. The aim of this study was to assess auditory outcome following aSAH and its relationship with cognition. A retrospective case-controlled study design was employed with aSAH cases and matched controls identified from the UK Biobank. Auditory and cognitive outcomes were assessed using the digit triplet test (DTT) and a test of psychomotor reaction time, respectively. Best DTT score was compared between cases and controls using the T test. A regression-based mediation analysis was performed to assess whether cognition mediated auditory outcome.270 aSAH patients with auditory outcomes were identified with an average follow-up of 106 months. A matched control cohort of 1080 individuals was also identified. The aSAH cohort had significantly impaired best DTT scores compared to matched controls (p = 0.002). Cognition significantly mediated auditory outcome following aSAH, accounting for 9.8% of the hearing impairment after aSAH. In conclusion significant hearing impairment follows aSAH. The deficit is bilateral and non-progressive. There is a link with cognitive deficit, pointing to a central rather than peripheral source, in keeping with an auditory processing disorder. All aSAH patients should be asked about hearing difficulty at follow-up and when present it should be investigated with peripheral and central auditory assessments, as well as cognitive tests.

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) accounts for 5% of all strokes with a case fatality of over 20%[1]. It has a disproportionately high socio-economic burden as it affects younger people than other stroke forms, with most survivors suffering significant neurological sequelae leading to decreased productivity, unemployment and cost to the economy[2]. The morbidity of aSAH includes functional[3], cognitive[4], psychological[5, 6] and auditory[7] deficits.

Auditory deficits significantly affect quality of life[8] and are relatively understudied in aSAH. A recent retrospective study involving 212 patients, suggested that 20% of aSAH patients presented with self-reported hearing difficulty post-aSAH[9]. While developing an aSAH specific outcome tool our group found that 21.4% of patients reported new onset hearing difficulty following aSAH[10], corroborating this finding. In a detailed case-control study (n = 41), we assessed aSAH patients identifying peripheral hearing loss and/or auditory processing disorder, using pure tone audiometry and a speech-in-noise test. Twenty-three percent of aSAH patients reported new onset hearing difficulty post-aSAH. Some peripheral hearing loss was present after aSAH, but the most striking finding was an auditory processing disorder[7].

The origin of hearing difficulty may be peripheral (if the cause resides within the auditory nerve or the outer/middle/inner ear) or central (when the pathology is within the central nervous system); the latter is known as auditory processing disorder (APD) or a central auditory processing disorder (CAPD)[11]. Individuals with APD characteristically present with listening difficulties (especially greater difficulty with hearing in background noise) yet the pure tone audiogram is normal. The pathology underlying APD may include afferent or efferent pathways of the central auditory nervous system (CANS), as well as other central networks that interact with the CANS (‘top down’ modulation), such as cognition[11]. For this reason, APD may co-exist with cognitive dysfunction. After aSAH, several pathological processes may damage peripheral and central auditory systems such as ischemia, inflammation, oxidative stress and iron deposition. In a study of 21 aSAH patients using magnetic susceptibility mapping of the auditory cortex we showed that all aSAH patients had detectable iron signal in the auditory cortex. This was more striking in those who experienced hearing difficulty, suggesting that the hearing difficulty found in aSAH patients may be mechanistically linked to iron deposition in the auditory cortex[7].

Cognitive deficits are common following aSAH influencing activities of daily living, quality of life and return to work[4]. Multiple domains of cognition are affected following aSAH including psychomotor, executive, visual and verbal memory/function[12]. Cognition is a key modulator of the CANS with cognitive deficits often found alongside APD[13]; it is thought that APD has both auditory and cognitive components[11]. However, no studies have yet simultaneously assessed cognition and auditory processing in aSAH patients to understand the relationship between the two. This has implications for management of APD after aSAH as patients may require both audiological and cognitive strategies. APD often co-exists with cognitive dysfunction[11] and this emphasises the importance of a combined approach when investigating and managing hearing difficulties reported by aSAH patients[7].

We recognised that further research looking at hearing and cognition in aSAH is needed and this would require larger sample sizes. The UK Biobank contains a cohort of aSAH patients and has detailed cognitive and auditory data on a subset of these individuals. The design, data collection and utility has been described in detail elsewhere[14]. We have demonstrated cognitive deficits in UK Biobank participants following aSAH with significant psychomotor deficits following aSAH compared to matched controls (manuscript under review).

The aims of this study were to: (1) compare auditory outcomes of individuals following aSAH and controls in the UK Biobank to identify evidence of hearing impairment following aSAH (i.e. in a larger sample); (2) assess the relationship between cognitive deficits and hearing impairment after aSAH.

Material and methods

This retrospective case-controlled study was conducted using the UK Biobank Resource under application ID49305, under national REC approval 16/NW/0274 and institutional approval (ERGO 49253). Reporting is in accordance with the STROBE statement for case-controlled studies[15]. The study uses information on 502,490 participants aged 40-69 recruited in the UK with informed consent between 2006-2010.

*Auditory outcome*

Auditory outcome was assessed in the UK Biobank with a speech-in-noise test, the digit triplet test (DTT)[16], the details of which have been published elsewhere[17]. Briefly, fifteen sets of three monosyllabic digits (e.g. 3-6-2) were presented with each ear tested separately. The digit triplets were presented in a background of noise shaped to match the spectrum of the speech stimuli. Noise levels varied adaptively after each triplet to estimate the signal to noise ratio (SNR) for 50% correct recognition of the three digits. The recognition threshold was taken as the mean SNR for the last eight triplets[16]. The DTT identifies hearing impairment with a view to onward referral for more comprehensive audiological assessment but does not differentiate between peripheral and central origin. The DTT is the only auditory measure done as part of the UK Biobank data collection. A higher (more positive) score represents worse hearing and is reported for each ear (data fields 20019 and 20021). The DTT score was considered as a continuous variable. In this study the best performing ear was used for the analysis in keeping with prior studies using the DTT in the UK Biobank[17].

*Cognitive outcome*

Cognitive outcome was assessed using a psychomotor reaction time test (data field 20023) where individuals press a button as soon as matching symbols are displayed on a digital screen. Other cognitive tests were available in the UK Biobank, but aSAH cases and controls significantly differed in psychomotor reaction time only[18].

*aSAH cohort*

aSAH cases were identified from the UK Biobank using hospital inpatient data (data fields 41271 and 41270), read code information from primary care data (data field 42040), and self-reported medical conditions (data field 20002) recorded at baseline or subsequent assessment centre visits (see Supplementary table 1 for ICD 9 and 10 inclusion codes).

For this study cases were included if the DTT was performed subsequent to the date of diagnosis of aSAH. Cases were excluded if there was evidence that the subarachnoid haemorrhage was non-aneurysmal in nature, such as trauma within 30 days of diagnosis of subarachnoid haemorrhage (see Supplementary table 1 for ICD 9 and 10 exclusion codes).

*Control cohort*

A single matched control cohort with DTT recorded at baseline assessment centre visit was identified from the UK Biobank using propensity score matching with a nearest neighbour method and a case: control ratio of 1: 4. The control population was matched according to variables known to influence auditory and cognitive outcomes in the UK Biobank:

1. Age at time of follow-up (data field 21003)
2. Townsend deprivation score (data field 189)
3. Sex (data field 31)
4. Education status dichotomised into individuals holding a college or university degree at time of assessment in the UK Biobank or not (data filed 6138)
5. Presence of medications known to influence psychomotor reaction time in the UK Biobank[19]
6. History of working in a noisy environment dichotomised into present or absent (data field 4825)
7. History of listening to loud music dichotomised into present or absent (data field 4836)

All data was considered as binary for the matching process apart from age and Townsend deprivation score which were considered as continuous. Individuals with missing data were excluded from the pool of individuals available for matching.

*Primary analysis*

T-test was used to compare the best DTT scores between cases and controls. In view of the large sample size, the central limit theorem applies allowing for parametric tests of the mean.

*Sensitivity analyses*

Both mean and worst DTT scores were compared between cases and controls with the T-test. Left and right ear DTT scores were also compared within case and control populations to assess for right ear advantage, which has been described in dichotic hearing tests though not typically seen on monaural hearing tests[20].

A further analysis was performed additionally matching the control population for ethnicity (data field 21000) which has been proposed to influence DTT scores in the UK Biobank[17]. This was conducted as a sensitivity analysis as there is missing ethnicity data in the aSAH cohort limiting sample size.

Time to follow-up in the UK Biobank is not standardised. A sensitivity analysis was therefore performed to assess whether time to follow-up in the aSAH cohort was a significant predictor of auditory outcome using linear regression with best DTT score as the dependent variable, controlling for the same seven variables as listed above.

In order to assess whether auditory outcome changes over time, the subset of post-aSAH and control participants with DTT assessments at two timepoints were compared to look for change in best DTT score using the paired samples Wilcoxon test. In the aSAH cohort both DTT assessments were after the aSAH.

*Mediation analysis*

To investigate whether cognition mediates auditory outcome, as assessed by the DTT, a regression-based mediation analysis was performed using PROCESS[21]. For this analysis aSAH status was considered as the independent variable, best DTT as the dependent variable and psychomotor reaction time as the mediator. Significance of the indirect effect of cognition on auditory outcome was tested using 5000 bootstrapped samples and 95% confidence intervals. Percent mediation was calculated as the indirect effect over total effect.

Analyses were performed in statistical software R (version 3.6.2, R Foundation for Statistical Computing) and SPSS Statistics (version 27.0, IBM Corporation). A p value of <0.05 was considered significant.

Results

888 aSAH patients were identified from the UK Biobank, of which 270 individuals had auditory outcome data. See Figure 1 for flow chart of inclusion of patients and Table 1 for demographics and data availability of aSAH patients. The mean follow-up time was 106 months (range 1-493 months) with 95% of aSAH patients being followed up after one year.

160,385 individuals were available in the UK Biobank with auditory outcome data to generate the matched control population. A single matched control population was generated (n = 1080) with a standardised mean difference <0.035 for all variables.

*Hearing impairment after aSAH*

The aSAH cohort had significantly impaired best DTT scores compared to the matched controls (aSAH: -6.88, control: -7.38, t = 3.05, p = 0.002). In multivariable linear regression analysis time to follow-up was not a significant predictor of best DTT score in the aSAH cohort (p = 0.42).

In the sensitivity analyses both mean and worst DTT scores were significantly impaired between the aSAH and control cohorts (mean aSAH: -6.10, mean control -6.63, t = 3.20, p = 0.001; worst aSAH: -5.31, worst control: -5.89, t = 3.05, p = 0.002). Compared to the control cohort additionally matched for ethnicity the aSAH had significantly impaired best DTT scores (aSAH: -6.94, control: -7.25, t = 2.03, p = 0.043).

There was no difference in DTT scores between right and left ear in either the aSAH (left: -6.06, right: -6.13, t = -0.43, p = 0.655) or control cohort (left: -6.66, right: -6.61, t = 0.78, p = 0.433) suggesting that both ears deteriorate equally following aSAH as opposed to this being a focal unilateral change.

*Hearing impairment after aSAH is fixed at late follow up*

Twenty post-aSAH patients and 124 control participants had DTT assessments at two timepoints. In the aSAH cohort these time points were both following aSAH. The average interval between DTT assessment was 71 months for the aSAH cohort and 86 months for the control cohort. There was a significant deterioration in best DTT score in both the aSAH (mean first DTT: -7.90, mean second DTT: -6.28, p = 0.001) and the control cohort (mean first DTT: -7.53, mean second DTT: -6.31, p < 0.001). There was no significant difference in change in DTT score over time between the aSAH and control cohorts (p = 0.97).

*Cognition and hearing*

Psychomotor reaction time was significantly slowed in the aSAH compared to the control cohort (aSAH: 589ms, control: 566ms, t = 2.22, p = 0.027). In the mediation analysis the odds ratio of the direct effect of case/control status on best DTT score was 0.46 (95% confidence interval 0.21-0.71). The indirect effect mediated by psychomotor reaction time was significant with an effect size of 0.05 (95% confidence interval 0.009-0.096) (see Figure 2). Cognition significantly mediated auditory outcome following aSAH, accounting for 9.8% of the hearing impairment after aSAH.

aSAH patients with severe auditory and cognitive deficits were identified if their DTT score and psychomotor reaction time were greater than two standard deviations above the mean of the control cohort (Table 2). Of the 21 aSAH patients with very poor auditory outcome, only two patients (10%) had pronounced cognitive issues as measured with psychomotor reaction time.

Discussion

In this large study of auditory outcome following aSAH, we confirm the presence of significant hearing impairment following aSAH, compared to matched controls, at an average follow-up of 106 months. We also demonstrate that cognitive deficits following aSAH, as measured by psychomotor reaction time, mediate a significant proportion of this hearing impairment.

Although the DTT is unable to differentiate between central and peripheral hearing impairment the fact that cognitive deficits mediate a significant proportion supports the previous findings that central origin hearing impairment plays an integral role in hearing deficits following aSAH[7]. The addition of PTA and brainstem auditory evoked responses would provide information on the relative contributions of peripheral and central hearing impairment following aSAH, however, it is not available in the UK Biobank. This is a limitation of this retrospective study. PTA and brainstem auditory evoked responses should be included in future prospective studies to further investigate the role of central and peripheral components to hearing impairment following aSAH. As stated earlier, the DTT identifies hearing impairment with the view of onward referral for more comprehensive audiological assessment. In addition to PTA, tests of APD and other more ‘real world’ measures including roving speech in multi-speaker babble, localisation and tracking of speech using a 180 or 360 degree rig, as well as a test of listening effort should be considered.

Cognitive deficits mediate a significant proportion of hearing impairment following aSAH with psychomotor reaction time significantly slower in the aSAH cohort compared to controls. However, the prevalence of cognitive impairment in aSAH patients with pronounced hearing difficulty was relatively low (10%, and quite similar to patients without pronounced hearing difficulty, see Table 2), suggesting that although cognition is an important contributor, other mechanisms play an integral role in hearing impairment after aSAH. A number of pathophysiological mechanisms have been proposed to underlie auditory deficits following aSAH including ischemia secondary to vasospasm[22] and more globalised pathology such as iron deposition in the cortex secondary to blood breakdown[7]. In this study we demonstrate that both ears deteriorate equally following aSAH supporting the theory that a more generalised process such as iron deposition is likely to be integral to hearing impairment following aSAH. Iron deposition can lead to both central and peripheral hearing deficits[23] and we are not able to differentiate between the two in this study.

Our previous study using both PTA and the Bamford-Kowal-Bench (BKB) speech-in-noise test demonstrated the presence of APD or central hearing impairment following aSAH[7]. The BKB test used had a fixed signal-to-noise ratio compared to an adaptive signal-to-noise ratio as in the DTT used here. The adaptive signal-to-noise ratio is thought to be more reflective of the real world auditory environment and consequently the results of this study confirm previous findings in a situation more comparable to real life emphasising the implications of these deficits to patients following aSAH.

A number of cognitive domains have been associated with APD including memory, language executive function and fluid reasoning[11, 24]. In this study we have used a measure of psychomotor reaction time as the cognitive outcome as this is the only cognitive domain in the UK Biobank which has been shown to differ between aSAH cases and controls[18]. Although this cognitive measure has been shown to correlate with deterioration in DTT[25], it may not be the most sensitive cognitive assessment to identify a significant relationship between cognitive deficits and hearing impairment following aSAH. Alternative cognitive tests may demonstrate a stronger association between cognition and auditory outcomes following aSAH and future studies should consider a comprehensive battery of cognitive assessments covering a range of cognitive domains to further explore this.

The World Federation of Neurological Surgeons (WFNS) grade is the strongest known predictor of clinical outcome following aSAH[26]. WFNS is not available in the UK Biobank, however, a subset of patients have length of stay (LOS) data which is strongly associated with WFNS[27]. When LOS is included as a predictor of best DTT score using linear regression including the other covariates controlled for above it is not a significant predictor of auditory outcome (p = 0.315). This is in keeping with our previous study which did not identify WFNS as a significant predictor of BKB or PTA[7]. Consequently, the lack of WFNS data is unlikely to influence the outcome of this study. Hearing aid use is available in the UK Biobank and 7 individuals in the aSAH cohort reported using a hearing aid (2.6%). When hearing aid use is included in a linear regression controlling for all other covariates it is not a significant predictor of auditory outcome (p = 0.525) and therefore unlikely to influence the results of this analysis.

Repeat DTT scores post-aSAH are only available for a small subset of the aSAH patients in the UK Biobank and demonstrate a deterioration in DTT over time following aSAH. This deterioration is not limited to the aSAH cohort with the same deterioration identified in the control cohort. The auditory deficit after aSAH therefore appears fixed, without recovery or progression, at late follow up (90% of aSAH cases with repeat DTT had both tests more than one year after aSAH). This contrasts with Kang who reported that 5 out of 8 cases of hearing impairment following aSAH completely normalised at 3-6 months[28]. This difference is likely explained by the much longer interval between DTT assessments in our aSAH cohort (mean 71 months) suggesting that the progressive deterioration is not a result of aSAH but rather more likely associated with aging (presbycusis). An age-related deterioration has been shown previously, specifically in speech-in-noise tests such as the DTT[29]. Future studies should include serial auditory assessments to allow more detailed evaluation of how auditory outcomes change over time.

*Clinical implications*

Hearing impairment has been shown to significantly impair quality of life[8]. The results of this study emphasise that aSAH patients should be asked about hearing difficulty during follow-up and those reporting hearing difficulty should be assessed using tests of both peripheral and central hearing, in addition to cognitive assessments.

APD after aSAH may require both audiological (assistive listening devices, listening environment modification, auditory training and compensatory strategies)[11] and cognitive rehabilitation. In addition, hearing aids should be considered for those identified with peripheral hearing loss. APD often co-exists with cognitive dysfunction[11] and this emphasises the importance of a combined approach when investigating and managing hearing difficulties reported by aSAH patients[7].

Cognitive assessment is essential given cognitive deficits contribute to hearing impairment post-aSAH. This is important given cognitive training can improve auditory outcomes and quality of life[30], and therefore should be considered in the management of hearing impairment. Additionally, cognitive assessment in conjunction with audiological assessment is beneficial as both cognitive dysfunction and hearing impairment may be over diagnosed when tested in isolation, resulting in less appropriate interventions[11].

Conclusion

Significant hearing impairment follows aSAH. The deficit is bilateral and non-progressive. There is a link with cognitive deficit, pointing to a central rather than peripheral source, in keeping with an auditory processing disorder. All aSAH patients should be asked about hearing difficulty at follow-up and when present it should be investigated with peripheral and central auditory assessments, as well as cognitive tests.

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**Fig 1.** Flow diagram for identification of aSAH patients from the UK Biobank

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**Fig 2.** Mediation analysis. Effect sizes (regression coefficients, β) reported for a: dependent variable on mediator; b: mediator on dependent variable, controlling for independent variable; c’: independent variable on dependent variable; m: indirect effect of the independent variable on the dependent variable, via the mediator. For the analysis aSAH case and control were coded as 1 and 0 respectively. \* indicates p<0.05.

Tables:

|  |  |
| --- | --- |
| Sample size | 270 |
| Age at time of follow-up Mean (±SD) yearsRange | 58 (±7)40-74 |
| Sex | F: 169 (63%)M: 101 (37%) |
| Source in UK BiobankICD-10ICD-9Self-reportedGP records | 20005515 |
| Time to follow-upMean (±SD) months | 106 (±95) |
| Length of stayMedian (IQR) daysMissing | 6 (2-13)70 |
| Townsend deprivation scoreMean (±SD) | -1.05 (±2.94) |
| Education statusCollege or university degree (good outcome) (%) | 85 (31%) |
| Medication statusMedications influencing psychomotor speed test scores (%) | 206 (76%) |
| History of working in a noisy environment (%) | 55 (20%) |
| History of listening to loud music (%) | 27 (10%) |

Table 1. Demographics of aSAH patients included in study. SD: standard deviation. IQR: interquartile range. GP: general practitioner. ICD: International Classification of Diseases

|  |  |  |
| --- | --- | --- |
|  | Best DTT normal (n=249) | Best DTT >2 SD from mean of controls (n=21) (DTT score >-4.07) |
| Psychomotor reaction time normal | 222 (89%) | 19 (90%) |
| Psychomotor reaction time normal > 2 SD from mean of controls (reaction time >792ms) | 22 (9%) | 2 (10%) |
| Missing | 5 (2%) | 0 (0%) |

Table 2. Frequency of severe cognitive and auditory deficits in the aSAH cohort. SD: standard deviation, DTT: digit triplet test.

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