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Research Article

A Single-Centre Retrospective Study on Cerebral Angiogram (DSA) Negative Subarachnoid Haemorrhage (SAH): Does Patient Co-Morbidity Affect the Likelihood of a Positive Repeat DSA?

Muzzammil Hussain[1]*, Zhaosheng Jin[1], Dina Ridwan[1], Sanjiv Chawda[2], Shahram Derakshani[2] and Babak Arvin[1]

[1]Department of Neurosurgery, Essex Neuroscience Centre, Queen's Hospital, Romford, Essex Rom Valley Way, Romford, England, UK

[2]Department of Neuroradiology, Essex Neuroscience Centre, Queen's Hospital, Romford, Essex Rom Valley Way, Romford, England, UK

***Corresponding Author:** Muzzammil Hussain, Department of Neurosurgery, Essex Neuroscience Centre, Queen's Hospital, Romford, Essex Rom Valley Way, Romford, England, UK.

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Abstract

Background and Purpose: In 10 - 20% of patients, admitted with subarachnoid hemorrhage (SAH), no underlying vascular cause is found. The purpose of the study was to identify the number of patients with SAH, whom had a primary negative-cerebral angiogram (DSA) and then went on to have a repeat positive-DSA. Secondly, whether patient specific variables could be identified, for the latter, for clinical prioritization of cases, monitoring patients and assessing outcomes.

Materials and Methods: A retrospective study was performed from March 2014 - March 2017, of patients admitted with SAH. The inclusion criteria were any patient with SAH 1) who had an initial negative DSA and 2) subsequently underwent a repeat DSA. All patients were scored with both the Fisher Grade Score (FGS) and World Federation of Neurosurgical Societies (WFNS) grade. Patient co-morbidities were collated and a previously validated, Charlson Co-Morbidity Index score (CIS) was assigned.

Results: We identified 50 (n) patients with an initial negative DSA, who underwent a repeat DSA. Only 10%, on repeat DSA (n = 5) had an underlying vascular pathology, and only 6% (n = 3), had an underlying aneurysm. The median FGS in the positive and negative repeat-DSA groups were 4 and 3, respectively ($p < 0.05$). The median WFNS score was 1 in both groups. The median CIS was 0, in both groups ($p > 0.5$).

Conclusions: Patients presenting with a higher FGS are more likely to have an aneurysm on repeat DSA. No other patient specific variables suggestive of a positive repeat-DSA could be identified. Repeat DSA should be considered as routine, as an underlying aneurysm could be left untreated even in those with low fisher scores.

Keywords: *Aneurysm; Co-Morbidity; DSA; Fisher; Subarachnoid Hemorrhage*

Introduction

Subarachnoid haemorrhage (SAH), secondary to intracranial aneurysm rupture is a severely debilitating condition affecting 10.5/100,000 people per year [1]. Patients undergo, computed tomography angiogram (CTA), initially to identify a vascular lesion [2]. However, the 'gold standard' assessment is catheter cerebral angiography (DSA) [2]. Patients thereafter may undergo endovascular or surgical treatment of the aneurysm [2]. Despite undergoing the initial DSA, in the literature, 10 - 20% of patients admitted with SAH, no underlying vascular cause can be identified [2].

The mortality associated with SAH ranges from 32 - 62% [1]. Therefore, it becomes pertinent to try to identify, if there is an underlying vascular cause for the SAH that can be treated to prevent a re-bleed [1]. Following discussion in neurovascular multi-disciplinary meetings, most, if not all patients with an initial negative-DSA will undergo a repeat DSA [3]. The repeat angiogram may be performed from 1 week to up to 6 weeks following the initial SAH ictus [4]. The reasoning behind this is that DSA is fluoroscopic examination of the intracranial vessels and an acute bleed and subsequent intracranial hematoma may obscure fine detail and fluoroscopic detail [4]. In the literature, patients with an initial negative DSA, subsequent DSAs may demonstrate either aneurysms, vasculopathies, arteriovenous malformations (AVM) or dural arteriovenous fistulas (dAVF) [5]. Currently no guidelines or criteria exist to identify those patients that should undergo repeat DSA [3]. However, it has been previously reported that repeat DSA can be, more or less clinically valuable, in particular haemorrhage patterns [6], with some suggesting that repeat DSA is more valuable in mesencephalic subarachnoid haemorrhage (MSAH) patterns as opposed to peri-mesencephalic (PMSAH) patterns [6]. Furthermore, to assess SAH, at presentation, two grading systems exist. Firstly, the WFNS (World Federation of Neurosurgical Societies) grading (I-V), relies upon the initial Glasgow Coma Scale (GCS) at presentation and the concurrent neurological deficit [7] is more relevant for assessing morbidity and mortality whilst the Fisher Grading Score (FGS) (I-IV), which relies upon the haemorrhage pattern seen on CT imaging [8], is more relevant to predicting complications such as cerebral vasospam (CVS) [8], which can affect the ability of DSAs to detect vascular pathology [4].

Aim of the Study

The aim of this study was to identify the proportion of patients, in our cohort, who initially had a negative DSA and went on to have a positive repeat-DSA [1-4]. Furthermore, whether from these patients, any patient related variables could be identified that would enable us to stratify and select patients who we should perform a repeat DSA on.

Methodology

A retrospective cohort study was performed for the period between March 2014 - March 2017, identifying all patients who were admitted with SAH in the Essex Neurosurgical Centre, Queen's Hospital. The inclusion criteria for the study was that the patient was admitted with SAH, regardless of WFNS Grade [8] or Fisher Grade (FGS) [9] and underwent an initial DSA, which was negative and thereafter also underwent a repeat-DSA. Patients who did not undergo a repeat-DSA were excluded from the study. All patients included in the study were 18 years old and above, and there was no upper age limit.

The clinical notes for each patient were reviewed, to identify patient demographics, any co-morbidities and smoking status. Patients' baseline co-morbidities were scored using the Charlson Co-Morbidity Index Score (CIS). The CIS is a validated scoring system that includes a comprehensive analysis of co-morbidities and populates a 10-year predictive survival [9]. All initial CT head scans, performed with standard protocol, and their associated reports by a Consultant Neuroradiologist were reviewed, to assess the patient's blood load, which subsequently gave rise to the FGS. The GCS and neurological deficit on initial presentation was also recorded and was used to identify the WFNS grading.

All cerebral angiogram (DSA) reports were obtained from the electronic patient archiving and communications system (PACS). All primary DSAs were double-reviewed by both a Consultant Neuro-radiologist and Consultant Neurosurgeon to ensure pathology was not overlooked, and to ensure that it was a true false-negative primary DSA study. This was checked against the hand written reports filed in the patients' notes to check corroboration between the reports on the PACS system and notes. Group data comparisons, between the repeat DSA-positive and DSA-negative groups were performed using non-parametric statistical tests, with a commercially available statistical package.

Results

In the study a total of 50 patients were identified, who underwent a repeat DSA following an initial negative primary DSA. When we analysed the data we found that the mean age of patients, in both the repeat DSA-negative and positive groups was 56. The age range in

the negative repeat DSA group was (33 - 78) and in the positive group was (31 - 68). There was a higher proportion of male (n = 31) to females (n = 14) in the negative DSA group, however in the positive repeat DSA groups there was a higher proportion of females (n = 4) as compared to males (n = 1) (Table 1).

	Repeat DSA-negative patient group	Repeat DSA-positive patient group	
Total patients (n)	45	5	
Vascular malformation		Aneurysmal	Non-aneurysmal
		3	2
Age - Mean	56 (33 - 78)	56 (31 - 68)	
Male (n)	31	1	
Female (n)	14	4	
Hypertension (n)	20	2	
Smoking (n)	7	2	
Median Fisher Score (whole group)	3	4	
Median Fisher score of aneurysmal and non-aneurysmal DSA-positive patients		Aneurysmal	Non-aneurysmal
		4	2
Lowest Fisher Score	1	1	
Median WFNS score	1	1	
Lowest WFNS Score	1	1	
Charlson-Index Score (CIS)			
Median	0	0	
Scored 0 points (n)	35	4	
Scored 1 point (n)	7	1	
Score 2 points (n)	3	0	

Table 1: *Summary of demographic, morbidity and patient characteristics of those admitted with SAH and have undergone a repeat diagnostic cerebral angiogram (DSA).*

Repeat DSA was negative in 45 patients and was found to be positive in 5 patients, with 3 patients demonstrating an underlying aneurysm. In two patients another underlying vascular pathology was found (n = 2); one case demonstrated an underlying dural arteriovenous fistula (dAVF) and another demonstrated an arteriovenous malformation (AVM). The average number of days between the primary DSA and repeat DSA was 13 days (range 8 - 14).

The median WFNS grade amongst the repeat DSA negative patients was 1 (n = 45). The median WFNS grade in positive repeat DSA patients was also 1 (n = 5).

There was no statistical difference in the WFNS grading between those with a positive DSA (n = 5) and negative DSA (n = 45) ($p > 0.05$). The median fisher score amongst negative repeat DSA patients was 3. In those with a positive repeat DSA, the median fisher score was 4. This difference was statistically significant ($p < 0.05$). The lowest fisher and WFNS score for each patient group was 1. The median Charlson-Index Score (CIS) was 0 in both groups.

Our data demonstrates that only 10% (n = 5) of individuals who had a repeat DSA (n = 50) demonstrated an underlying pathology in our study and only 6% (n = 3) had a demonstrable underlying aneurysm. Differences in age, Charlson co-morbidity index, and smoking

were found not to be significant between the positive and negative DSA groups ($p > 0.05$). The range of CIS in the negative and positive-repeat DSA groups were 0-2 and 0-1, respectively. Only 40% (n = 2) of repeat DSA-positive patients were smokers or had diagnosed hypertension. Interestingly, more patients were hypertensive (n = 20) in the repeat DSA-negative group (44%), as compared to the repeat DSA-positive groups (n = 2) ($p < 0.05$) (Table 2).

	Total patients(n)	Repeat DSA-negative patient group (n)	Repeat DSA-positive patient group (n)
Hypertension	22	20	2
Smoking	9	7	2
Diabetes	4	0	0
Liver disease	0	0	0
Malignancy	0	0	0
AIDS (acquired immunodeficiency syndrome)	0	0	0
CKD (chronic kidney disease)	0	0	0
Congestive heart failure (CHF)	0	0	0
Myocardial infarction (MI)	2	2	0
COPD (chronic obstructive pulmonary disease)	1	0	1
PVD (peripheral vascular disease)	0	0	0
CVA or TIA (cerebrovascular accident or transient ischemic attack)	0	0	0
Dementia	0	0	0
Hemiplegia	0	0	0
Connective tissue disease	1	1	0
Peptic ulcer disease	1	0	0
Alcohol Excess*	0	0	0

Table 2: *Summary of co-morbidities of patients in repeat DSA-negative and DSA-positive groups.*
**Defined as more than 14 units a week.*

Discussion

To our knowledge this is the first study to comprehensively investigate the co-morbid status of patients presenting with SAH who have an initial negative primary-DSA and have a subsequent repeat DSA, to rule out an underlying vascular cause for their SAH. Our study demonstrates that we are reporting a similar incidence of patients with repeat DSA-negative SAH, as has been previously cited in the literature [1-4]. Only 10-20% of patients with an initial negative-DSA, go onto have a positive-DSA identifying any underlying vascular lesion [5]. In our present study the percentage of those patients who subsequently had an underlying aneurysm on repeat-DSA was only 6% (n = 3). Part of the contributing factor for this low incidence could be due to the increased diagnostic yield of DSA as practice currently, due to technological advancements in fluoroscopy, such as 3-D visualisation and image reconstruction [3]. This has certainly been seen over the last two decades, with a marked reduction in the false-negative rates of primary DSA, with the incidence of positive repeat DSAs falling from 46%, in the pre-2000s era to 10 - 20% in more recent literature [3,5].

The risk factors typically associated with aneurysmal SAH, include; being female, over 50, a smoker and suffering from hypertension [10]. The median age for our repeat DSA-positive cohort was 56, with a greater number of females demonstrating an underlying vascular malformation, corroborating aneurysmal SAH risk-factor data [1].

Our study suggests that a similar etiology; hypertension and smoking status may be a contributing factor for both SAH caused by aneurysmal rupture [10,11] and in those with unknown etiology [12]. Similar to previous studies, we demonstrated that non-aneurysmal SAH (NASAH) occurs more frequently in men, than women [12,13], therefore it is possible that physiological processes unique to the male gender is a contributing factor for NASAH, whilst oestrogen is thought to contribute to the increased risk of aneurysmal SAH (ASAH) in women [12,13]. These findings, of a greater proportion of males, suffering from NASAH, need to be elucidated further in large population based epidemiological studies [13].

The exact mechanisms of how risk factors such as hypertension and cigarette smoking contribute to SAH are not clearly understood [14,15]. However, inflammatory changes and hemodynamic forces on cerebral vasculature, directly as a result of smoking and hypertension, are reported to contribute to the aetiology [14,15]. In ASAH, a definitive management such as endovascular coiling or surgical clipping can be offered, with further risk-factor modification [1]. In contrast, risk-factor stratification seems to be the only modifiable factor, in the clinical management of NASAH to prevent a risk of re-bleed and improve clinical outcomes [16].

In our study we preferred categorisation of our patients' SAH bleeding patterns, into Fisher Grading Scores (FGS) as opposed to the peri-mesencephalic (PMN) and mesencephalic SAH (MSAH), contrary to previous studies [3-6,17]. In our centre, patients with typical perimesencepahlic bleeding patterns, do not always go onto have repeat DSA, with a decision not to proceed, being taken by a multi-disciplinary team consisting of interventional neuro-radiologists and vascular neurosurgeons, as has been previously reported [3].

For some time, it has been known that a higher FGS indicates a greater risk of cerebral vasopasm (CVS) [8]. Those patients with a larger bloods load, have a higher FGS [8], which makes fluoroscopic assessment particularly difficult in these patients, as acute blood may obscure the fine detail of the vasculature [4]. CVS, itself can cause obscuration of vessels and can even occur in 4 - 16% of patients with PMSAH, with a small blood load [3-6,18,19]. By utilizing the FGS, even a low score, captures both suspicious PMSAH and MSAH blood patterns, as between 14.0 - 48% of patients graded with FGS, based on their blood pattern, develop CVS as compared to the lower range of 15.5 -26.5% of patients, if PMSAH and MSAH grading alone is used [18].

In this study, the median FGS for those patients with a repeat positive-DSA was higher (FGS-4) as compared to the repeat DSA-negative group (FGS-3) ($P < 0.05$). In our cohort we could not demonstrate an aneurysmal cause for SAH in those with an FGS of less than 4, where the FGS indicated a diffuse SAH pattern or intraventricular hemorrhage (IVH). This is corroborated by previous studies wherein, a higher incidence of aneurysms (17%) was demonstrated in those with a diffuse SAH pattern, on repeat-DSA, following an initial negative one, as compared to patients with a lower blood load [5]. A diffuse blood pattern scores higher on the FGS, than a localised SAH blood pattern, except in cases of IVH [8].

Using a combination of both grading systems, for future studies, to us seems to be the most optimum method for prioritising cases for DSA, planning definitive treatment, and monitoring patients clinically [18,19]. Even in NASAH, the FGS, can be utilised to determine patient outcomes, in terms of the assessing the risk of developing CVS, hydrocephalus and delayed cerebral ischemia (DCI), and also determining the eventual functional outcome and mortality rate [18,19].

In this study we were unable to elucidate any other variable by which we could determine those patients appropriate for a repeat-DSA, following an initial negative one. This is because the majority of patients in our cohort were generally, in good health with a few co-morbidities (Table 2). On review of the clinical records of our patient series, no patients were recorded to have a diagnosis of alcohol excess, however details regarding recent or current alcohol use were not recorded. Few previous studies have described the co-morbid status of DSA-negative SAH patients in detail [12,17], with studies mainly reporting on gender, hypertension and smoking status [2-6,18,19]. Our present study is therefore a valuable contribution, describing the patient characteristics of this particular group of patients.

The limitations of our study are that our analysis identified a small series (n = 50) of patients whom underwent a repeat-DSA. This study only yielded 5 patients who went on to have positive repeat DSAs, and even fewer that had an underlying aneurysm. Patients were

only categorised into FGS rather than both FGS and PMSAH and MSAH blood patterns. We only retrospectively investigated 3 years of clinical records; a longer time frame may have identified further patients, for analysis. A future multi-center prospective study may identify a larger cohort of patients, with possible variability between repeat negative and positive -DSA patients, by which the initial aim of the study can be met.

Conclusion

SAH can be a debilitating condition. In the majority of patients an aneurysmal cause is found. In a small percentage of patients (10-20%), no underlying vascular malformation is found and in an even smaller percentage of patients, an aneurysm may become apparent on repeat-DSA. The decision to proceed to repeat DSA, is still reliant upon clinician experience and the quality and confidence in the primary DSA, being a true-negative. Current FGS, PMSAH and MSAH grading systems for SAH, may be useful in identifying those patients who are likely to have an underlying vascular lesion, and to prioritise these patients, and decide if and when best to perform repeat-DSA. Furthermore, these grades can be used comprehensively, for medical monitoring of patients for complications, related to the SAH and also preventing poor functional outcomes and reducing mortality. In our study we were not able to identify any patient related morbidity variables that would enable us to identify which patients would go onto have a repeat positive DSA after their initial negative DSA. Our study has clear limitations, including a small patient series and a short study period. Therefore, future longitudinal multi-centre, retrospective or prospective studies are required to investigate this question further.

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Declarations

The authors have no conflicts of interests to declare.

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