

Non-traumatic non-aneurysmal subarachnoid haemorrhage: Single institutional experience

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Abstract

Aim: Despite the advanced diagnostic methods we use today, the rate of negative digital subtraction angiography (DSA) is 15% in patients diagnosed with subarachnoid hemorrhage (SAH), and these types of hemorrhages are named as non-aneurysmal (NASAH). Various factors such as inadequate interpretation of the beginning angiography, vasospasm, thrombosis, intra-cerebral hematoma pressure may cause DSA to be negative. This study aims to determine the causes of bleeding in patients who were suffered from NASAH.

Materials and Methods: The study evaluated 664 patients with SAH from 2010 to 2016. DSA was performed on these patients within the first 3 or 6 hours. Sixty-seven patients with DSA negative were included in the study group. The patients were divided into three groups as perimesencephalic subarachnoid hemorrhage (PMSAH), non-perimesencephalic subarachnoid hemorrhage (nPMSAH), CT negative subarachnoid hemorrhage (CT negative SAH). These three groups were evaluated based on age, gender, Glasgow coma scale (GCS), World Federation of Neurosurgical Societies (WFNS) grade, Hunt and Hess Classification and Fisher's scale, hospitalization time duration, complications and computerized tomography (CT), and cervical and cranial MRI was performed on patients without correlation between DSA results if needed.

Results: Of the 664 patients diagnosed with SAH, 67 (10.09%) had NASAH. Statistically significant differences were found between CT Negative SAH and PMSAH and CT Negative SAH and nPMSAH in terms of the variables of GCS during hospital admission and total duration of hospitalization. Statistically significant differences were found between CT Negative SAH and PMSAH and nPMSAH in terms of the variables of GCS during hospital discharge. There were statistically significant differences between the types in terms of WFNS Classification, Hunt and Hess Classification and Fisher's Scale.

Conclusion: We believe that this study will contribute to the literature about the necessity of performing additional radiologic imaging during clinical follow-up since belated diagnosis in patients with NASAH may increase mortality.

Keywords: CT Angiography; DSA; non-aneurysmal; subarachnoid haemorrhage

INTRODUCTION

The most common reason for non-traumatic subarachnoid hemorrhages (SAH) is aneurysm (1). Although computerized tomography (CT) is the most commonly used radiological method in the diagnosis of SAH, magnetic resonance imaging (MRI), performing lumbar puncture (LP) in suitable patients, observing erythrocyte in the cerebrospinal fluid (CSF) is also used in the diagnosis. The diagnosis methods in SAH are computerized tomography angiography (CT angiography), MRI angiography, and digital subtraction angiography (DSA) (2, 3). Despite the advanced diagnostic methods, the rate of detecting no aneurysms with DSA is 15% in patients diagnosed with SAH, and these types of bleedings are

named as non-aneurysmal subarachnoid hemorrhage (NASAH) (1,4,5). The probability of occurrence of aneurysm in the follow-up DSA examination of the patients with NASAH is 4% (2). Types of NASAH are divided into three as perimesencephalic subarachnoid hemorrhage (PMSAH), non-perimesencephalic subarachnoid hemorrhage (nPMSAH), CT negative subarachnoid hemorrhage (CT negative SAH) (6). While no bleeding is observed in patients with CT negative, PMSAH is the SAH occurring in prepontine and/or perimesencephalic region while nPMSAH is the SAH occurring in other regions (7). The rate of vasospasm occurrence in patients with CT negative and PMSAH is low and the clinical course is generally good. The clinical course is worse in patients with nPMSAH and aneurysmatic SAH but there is not much difference (8,

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9). This study intended to contribute to the clinical and radiological systematic in the investigation of bleeding causes in patients who were monitored due to NASAH.

MATERIALS and METHODS

Approval for this study was obtained from the Health Sciences Non-Interventional Clinical Research Ethics Committee of Inonu University with the decision numbered 2020/711. In this study, the diagnosis of SAH in patients with erythrocyte in LP (lumbar puncture), clinically sudden headache and neck stiffness was made with cranial CT and cranial MRI in the emergency service between 01.01.2010 and 01.01.2016. In total, 664 patients were evaluated. DSA was performed on these patients within the first 3 or 6 hours. Sixty-seven patients with DSA negative were included in the study group. The patients were divided into three groups as PMSAH, nPMSAH, CT negative SAH. These three groups were evaluated based on age, sex, clinically Glasgow coma GCS), WFNS Classification, Hunt and Hess Classification and Fisher's scale, duration of hospitalization in intensive care, hospitalization duration, complications and CBT, and cervical and cranial MRI was performed on patients without correlation between DSA results if needed.

Statistical Analysis

Quantitative data were given as median (minimum-maximum) while qualitative data were given as numbers (percentage). The suitability to normal distribution was assessed using the Shapiro-Wilk test. Since the variables of Glasgow Coma Scale values during hospital admission and discharge, duration of hospitalization in intensive care and the total duration of hospitalization did not show normal distribution ($p < 0.05$), Kruskal Wallis test was used to examine the differences between types. Pairwise comparisons after significant Kruskal Wallis H tests were

evaluated with Conover test. Pearson Chi-Square test was used to examine the correlations between types (CT negative, Perimesencephalic, Non-perimesencephalic) and WFNS Classification, Hunt and Hess Classification and Fisher's scale. Bonferroni corrected Pearson Chi-Square test was used in the binary comparisons of the types in terms of the variables. The statistical significance level was $p < 0.05$. IBM SPSS Statistics 26.0 program was used in the analyses.

RESULTS

Of the 664 patients diagnosed with SAH, 67 (10.09%) had NASAH. The number of patients with CT negative SAH was 8 (11.9%), and the number of patients with PMSAH was 29 (43.3%), and the number of patients with nPMSAH was 30 (44.8%). Of the patients, 39 (58.2%) were male, and 28 (41.8%) were female. The mean age for the patients was 52.46 ± 15.48 (range 24 to 90). Table 1 presents the descriptive statistics of Glasgow Coma Scale values during hospital admission and discharge, duration of hospitalization in intensive care and the total duration of hospitalization in terms of types (CT negative SAH, PMSAH, nPMSAH). There were significant differences between types (CT negative SAH, PMSAH, nPMSAH) in terms of Glasgow Coma Scale values during hospital admission and discharge, duration of hospitalization in intensive care and the total duration of hospitalization (Kruskal-Wallis test; $p < 0.05$) (Table 1). There are statistical differences between CT Negative, Perimesencephalic and Non-Perimesencephalic groups in terms of arrival Glasgow Coma Scale and Intensive Care Duration (Conover Post-Hoc test; $p < 0.05$). There was a significant difference between the CT Negative and Non-Perimesencephalic groups with respect to hospital discharge Glasgow Coma Scale and Total length of stay (Conover Post-Hoc test; $p < 0.05$) as shown in Table 1.

Table 1. The correlations between the variables of the Glasgow Coma Scale during hospital admission and discharge, duration of hospitalization in intensive care and the total duration of hospitalization

Variable (Median (Min-Max))	Type			p*
	CT Negative SAH (n=8)	PMSAH (n=29)	nPMSAH (n=30)	
GCS during hospital admission	15 ^{a,b} (12-15)	13 (7-15)	12.50 (3-15)	0.033
GCS during discharge	15 ^b (15-15)	15 ^b (15-15)	15 (0-15)	0.009
Duration of Hospitalization in Intensive Care	3 ^{a,b} (2-5)	5 (2-13)	7.50 (1-23)	0.025
Total Duration of Hospitalization	6 ^a (2-12)	12 (0-21)	10.50 (0-30)	0.035

*: Kruskal Wallis H test; ^a: It is different from the perimesencephalic group, ^b: It is different from the non-perimesencephalic group

Table 2 presents the number of the patients and column percentage in terms of WFNS Classification, Hunt and Hess Classification and Fisher's Scale of types (CT negative SAH, PMSAH, nPMSAH). There were statistically significant differences between the types in terms of WFNS Classification, Hunt and Hess Classification and Fisher's Scale (Pearson Chi-square test; $p < 0.05$). While there was a statistically significant difference between CT Negative SAH and PMSAH in terms of the 1st grade of

WFNS and Hunt and Hess Classifications ($p < 0.05$), there were no significant differences between the three groups regarding the other grades ($p < 0.05$).

While no complications emerged in 64 (95.5%) patients, hydrocephalus was observed in 1 (1.5%) patient died, 2 (2.9%) patients with nPMSAH and 1 (1.5%) patient with PMSAH. A shunt was needed in one of the patients with hydrocephalus. Follow-up DSA was not performed on

25 patients with no clinical and radiological vasospasm (patients without radiological vasospasm in the first DSA) and no feature in additional cranial imaging method. Of the patients on whom follow-up DSA was performed, 8 (11.9%) had aneurysm, 3 (4%) had posterior circulation aneurysm, and 5 (7.4%) had anterior circulation aneurysm. Aneurysm was detected on 3 (4%) patients with PMSAH and 5 (7.5%) patients with nPMSAH on whom follow-up DSA was performed. Vasospasm was detected on 20 (30%) patients in DSA. Of these patients, 1 (1.5%) had CT negative SAH, 6 (8.9%) had PMSAH and 13 (19.4%) had nPMSAH. MRI was performed in 17 patients (25%). Of these patients, 12 (18%) had nPMSAH, 4 (6%) PMSAH

and 1 (1.5%) had CT negative SAH. In all contrast, cranial MRI examinations, one of the patients with nPMSAH had a meningioma, and one patient had thrombosed aneurysm.

Cervical MRI was performed in patients with neck, back pain and neck stiffness that did not pass clinically. Cervical MRI was performed on 3 (4.5%) patients, and no feature was found. No aneurysm was detected in 2 (3%) patients with PMSAH who received CT angiography and the follow-up DSA of the same patients was positive. No aneurysm was detected in 3 (4.4%) patients with nPMSAH who received CT angiography, and the follow-up DSA of one of these patients was positive (Table 3).

Table 2. The number of patients and column percentages in terms of WFNS Classification, Hunt and Hess Classification and Fisher's Scale

Variable		CT Negative SAH	PMSAH	nPMSAH	Total
Number of Patients		8 (11.9%)	29 (43.3%)	30 (44.8%)	67
WFNS Classification	1	6 (75.0%)	8 (27.6%)	9 (30.0%)	23 (34.3%)
	2	1 (12.5%)	9 (31.0%)	5 (16.7%)	15 (22.4%)
	3	0 (0%)	0 (0.0%)	1 (3.3%)	1 (1.5%)
	4	1 (12.5%)	12 (41.4%)	9 (30.0%)	22 (32.8%)
	5	0 (0%)	0 (0.0%)	6 (20.0%)	6 (9.0%)
Hunt&Hess Classification	1	6 (75.0%)	2 (6.9%)	2 (6.7%)	10 (14.9%)
	2	1 (12.5%)	15 (51.7%)	11 (36.7%)	27 (40.3%)
	3	1 (12.5%)	6 (20.7%)	5 (16.7%)	12 (17.9%)
	4	0 (0.0%)	6 (20.7%)	5 (16.7%)	11 (16.4%)
	5	0 (0.0%)	0 (0.0%)	7 (23.3%)	7 (10.4%)
Fisher's Scale	1	8 (100.0%)	0 (0.0%)	0 (0.0%)	8 (11.9%)
	2	0 (0.0%)	29 (100.0%)	13 (43.3%)	42 (62.7%)
	3	0 (0.0%)	0 (0.0%)	7 (23.3%)	7 (10.4%)
	4	0 (0.0%)	0 (0.0%)	10 (33.3%)	10 (14.9%)

Table 3. TFollow-up DSA, DSA vasospasm, MRI, CT angiography and results

	Follow-up DSA Aneurysm	DSA Vasospasm	Brain MRI	Cervical MRI	CT Angiography
CT Negative SAH (n=8)	0	1 (1.5%)	1 (1.5%)	0	2 (3%)
PMSAH (n=29)	3 (4%)	6 (8.9%)	4 (6%)	1 (1.5%)	2 (3%)**
NPMSAH (n=30)	5 (7.5%)	13 (19.4%)	12 (18%)*	2 (2.9%)	3 (4.4%)***
Total (n=67)	8 (11.9%)	20 (30%)	17 (25%)	3 (4.5%)	7 (10.4%)

*NPMSAH cranial MRI examination revealed meningioma in one patient and thrombosis aneurysm in one patient, and it was determined as 2.9% in all patients with DSA negative

**The 2 CT angiographies performed in PMSAH was negative, but the follow-up DSAs were positive

***The 3 CT angiographies performed in NPMSAH was negative, but one follow-up DSA was positive

DISCUSSION

The most common reason for non-traumatic subarachnoidal hemorrhages (SAH) is an aneurysm. Despite the advanced diagnostic methods, the rate of detecting no aneurysms with DSA is 15% in patients diagnosed with SAH, and these types of bleedings are named as NASAH (1,4,5). PMSAH is when the bleeding center is just in front of the mesencephalon, when bleeding

sometimes spreads to the anterior part of the ambient cistern or the basal of the Sylvian cistern, when there is no bleeding in the anterior interhemispheric fissure and lateral Sylvian fissure and when intraventricular bleeding is not observed. NPMSAHs are the names given to subarachnoidal hemorrhages emerging outside this region (6,10). Although the risk of bleeding a few hours after SAH is high, it does not increase the risk of bleeding of early DSA

in normal blood pressure (11). No recurring bleeding after DSA was observed in our cases. No apparent lesions are observed in approximately 7-15% of the DSAs performed in the first examination of patients with subarachnoid hemorrhage (1,8). The percentage of patients with DSA negative and subarachnoid hemorrhage was 10.09% in the present study, and this result is similar to the relevant literature. Sex and age in patients with negative angiography and SAH should be discussed. Kong et al. evaluated 159 patients with SAH and included 12 patient groups and found that aneurysmal SAH was higher among female sex (12). Flaherty et al. reported that female sex and younger ages were higher (1). The rate of males was higher, and the mean age was 52 in the present study. Considering the WFNS Classification, GCS, Hunt and Hess Classification and Fisher's scale of all patients with negative angiography, the clinical picture was the best in patients with CT negative SAH followed with PMSAH and nPMSAH (5,13). The results in the present study are in line with the literature.

The mean hospitalization duration was the lowest in the PMSAH group (6.3 days) followed with CT negative SAH (10.1 days) and NPM-SAH (14.7 days) (5). The duration of hospitalization in intensive care was five days in PMSAH, three days in CT negative SAH and 7.5 days in NPMSAH. The total duration of hospitalization was 12 days in PMSAH, six days in CT negative SAH and 10.5 days in NPMSAH. There was a statistically significant difference between the duration of hospitalization intensive care and total hospitalization duration, and this show similarity with the literature. Therefore, clinical vasospasm of patients with CT negative SAH is considered to be rare in our series.

There were significant differences between PMSAH, CT negative SAH and NPMSAH in terms of the risk of vasospasm and hydrocephalus, clinical result and quality of life. Radiological vasospasm was reported more than clinical vasospasm. Coelho et al. observed radiological vasospasm in 33.3% of the patients with nPMSAH and 13.8% of the patients with PMSAH (14). Another study observed angiographic vasospasm in 25.7% of the patients with nPMSAH and 7.7% of the patients with PMSAH (13). The researchers observed radiological vasospasm in 1 (1.5%) patient with CT negative SAH, 6 (8.9%) patients with PMSAH and 13 (19.4%) patients with nPMSAH in the present study, and this result is lower than that in the literature. Hydrocephalus is observed at the incidence rate of 9-25% in PMSAH compared to nPMSAH (14-16). Hydrocephalus was observed in one (1.5%) patient with PMSAH in the present study (extra ventricular drainage was fixated) and shunt was not needed while shunt was needed in one (1.5%) patient with nPMSAH. GCS, WFN, Fisher, HH classifications are prognostic markers in determining the clinical course of the patient (17). In the present study, 3 patients who developed complications were those with high WFN, fisher and HH grade.

Various factors such as inadequate interpretation of the beginning angiography, vasospasm, thrombosis, intra-cerebral hematoma pressure may cause DSA to be negative.

Therefore, follow-up DSA, MRI and CT angiography should be performed to reveal the underlying reasons. Some studies asserted that noninvasive examinations such as CT and MR angiography could be used instead of DSA (18). The sensitivity is low in the determination of aneurysms smaller than 3 mm in neuroimaging tests such as CT and MR angiography (5,16,19). Aneurysm was observed in the follow-up DSA of most of the patients with CT negative angiography in the present study. This lowers the reliability of CT angiography. Aneurysm was detected at the rate of 12-15% in patients with NASAH with follow-up imaging methods in the literature (6,20). Aneurysm was found in parallel with the literature. In the case that no hematoma or vasospasm were observed in the first DSA of patients with NASAH, the follow-up DSA is not recommended (13). In a study conducted with 254 patients, no follow-up angiography was recommended in patients with PMSAH (21). It was reported in another series with 179 patients that the rate of positivity in the follow-up DSAs of patients with nPMSAH was 10% (22). Follow-up DSA was performed on 25 patients without any finding of clinical and radiological vasospasm and hematoma presence in the tomography and MRI regardless of groups and aneurysm was detected in 4% of the patients with PMSAH and 7.5% of the patients with nPMSAH in the present study. In some studies, 1.5% AVM was detected in cranial MRI examination, and no feature was detected in some other studies (5,16). In a series with 179 patients, all patients had negative MRI findings (22). The researchers observed thrombosis aneurysm in one patient and meningioma in one patient in the present study. Cervical AVMs show symptoms due to cerebral blood stealing, subarachnoid hemorrhage and mass effect. Therefore, the anamnesis of the patients is important. Recurrent neck pain and back pain are present, complaints such as hemiparesis, plegia, dizziness, syncope emerge (23,24). In a study conducted with 75 patients with DSA negative, spinal bleeding was observed in 3 patients and MRI was not recommended for all patients (25). In another series with 41 patients, MRI was performed on 13 patients and cervical spinal. AVM was observed in one patient (23). Cervical MRI was not performed on patients without symptoms in the present study and no features were obtained in the MRI results.

LIMITATIONS

There are limitations such as a small number of cases, a retrospective study, a single center, lack of control DSA in all patients, overlooked aneurysms smaller than 2 mm, and the reason for experience in CT angiography evaluation.

CONCLUSION

The clinical course in NASAH is generally right. However, it requires close monitoring owing to the possibility of vasospasm, hydrocephalus and recurrent bleeding, and it may show a mortal course. A useful evaluation of WFN, HH, Fisher and GCS in the first examination of these patients in the emergency room enables the prediction of the clinical and radiological course. Since determining the etiology of NASAH will decrease mortality, additional imaging methods other than DSA are significant. It is still discussed

whether to perform follow-up DSA, CT angiography, brain and cervical MRI on all patients. It will be appropriate to perform cranial MRI in patients with suspicious lesions in CT while performing cervical MRI will be appropriate in patients with neck stiffness, neck and back pain that do not pass and/or reduce. In conclusion, we conclude that this study will contribute to the literature about the necessity of performing additional radiologic imaging during clinical follow-up since belated diagnosis in patients with NASAH may increase mortality. Additionally, multiple evidence-based retrospective publications are needed to provide optimal diagnostic results.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: Approval for this study was obtained from the Health Sciences Non-Interventional Clinical Research Ethics Committee of Inonu University with the decision numbered 2020/711.

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