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Original Investigation

Clinical Course of Non-Traumatic Non-Aneurysmal Subarachnoid Hemorrhage: A Single Institution Experience over 10 Years and Review of the Contemporary Literature

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ABSTRACT

AIM: To report our experience with a relatively large series of patients with non-traumatic non-aneurysmal subarachnoid hemorrhage (NNSAH) to identify the prognosis associated with different bleeding patterns as well as a further diagnostic work-up to determine the underlying cause.

MATERIAL and METHODS: Between January 2004 and December 2014, 81 patients with angiography-negative non-traumatic subarachnoid hemorrhage (SAH) were treated at our institution. Diagnosis was confirmed with a typical history of spontaneous SAH and cranial computed tomography (CT) scan or lumbar puncture (LP). The patients were grouped according to the bleeding pattern on the CT scan: Group 1: Perimesencephalic (PM) SAH (n=33, 40.7%); Group 2: Non-perimesencephalic (nPM) SAH (n=41, 50.6%); and Group 3: CT-negative NNSAH (n=7, 8.6%). The clinical course, hospitalization period, and complications were noted. All patients underwent an initial four-vessel digital subtraction angiography (DSA). Cranial magnetic resonance imaging (MRI), repeat DSA investigations and spinal MRI were performed in all patients.

RESULTS: The mean hospital stays were 6.3, 14.7 and 10.1 days for patient groups 1, 2, and 3, respectively. The mortality rate was 1.2% (1 patient) in our series. Repeat DSA investigations were positive in two patients (2.5%), both from Group 2 (4.9%). Cranial MRI revealed 100% negative results. Spinal MRI revealed positive results in three patients from Group 2 (7.3%).

CONCLUSION: We suggest our diagnostic work-up for patients with nPM-SAH, namely repeat DSA and spinal MRI, until an evidence-based guideline is established for the patient management.

KEYWORDS: Non-aneurysmal subarachnoid hemorrhage, Negative angiography, Perimesencephalic, Non-perimesencephalic, Spinal magnetic resonance imaging, Digital subtraction angiography

INTRODUCTION

The majority of non-traumatic subarachnoid hemorrhage (SAH) events are caused by the rupture of saccular aneurysms, which are associated with significant morbidity and mortality (16). However, in approximately 15% of patients with non-traumatic subarachnoid hemorrhage, no underlying cause was detected on initial four to six vessel digital subtraction angiography (DSA) (13,21,31,48,52,54).

Although the clinical course of non-traumatic non-aneurysmal subarachnoid hemorrhage (NNSAH) has been reported to be

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benign compared with aneurysmal SAH, controversial results were reported regarding the bleeding patterns as observed in initial computed tomography (CT) scans. Among these bleeding patterns, pure perimesencephalic (PM) SAH is associated with lower complication rates, mild clinical course and better outcomes (3,4,23). PM-SAH was first defined by van Gijn et al.(55), and approximately one third to two thirds of these patients were reported to have this bleeding pattern (18,23,29). The remainder of the patients had different bleeding patterns on the initial CT scans, including sylvian, intraventricular, interhemispheric or convexal patterns. All of these bleeding patterns may be designated as non-perimesencephalic (nPM) SAH, and both the clinical course as well as the outcome of patients with nPM-SAH remains controversial (6,23,57).

Current controversies also include the necessity and diagnostic yield of further neuroimaging modalities in the clinical course of NNSAH, including repeat cranial DSA, cranial and spinal magnetic resonance imaging (MRI) and CT or MR-angiography (4,18,41,53).

In this retrospective study, we report our experience with a relatively large series of patients with NNSAH to identify the prognosis of patients with different bleeding patterns and to develop investigation protocols that can be used to determine the underlying cause.

MATERIAL and METHODS

Between January 2004 and December 2014, 81 patients with NNSAH were treated at the Department of Neurosurgery, Istanbul University, Istanbul School of Medicine. The files, hospital and outpatient clinic records were retrospectively reviewed. These 81 patients constitute 15% of all patients (n=525) who had been admitted with SAH during the study period. The diagnosis was confirmed via typical history, the clinical features of spontaneous SAH and blood observed in the subarachnoid space and/or the ventricles on the initial cranial CT scan. In scenarios involving the absence of blood on the initial CT scan and high clinical suspicion, lumbar puncture (LP) was performed, and the presence of the blood was confirmed with xanthochromia of the cerebrospinal fluid (CSF). NNSAH was categorized according to the Fisher and WFNS grading scales. The patients were divided into 3 groups according to the bleeding pattern on the initial CT scan:

1) PM-SAH

2) nPM-SAH

3) CT-negative NNSAH.

All patients underwent an initial four-vessel DSA. All patients underwent cranial MRI for the early recognition of possible underlying causes. Repeat DSA investigations were performed 7 to 21 days following the initial DSA. Radiological vasospasm (VS) was considered to be the segmental vasoconstriction of cerebral arteries as shown via DSA. Clinical vasospasm was considered to be acute and severe headache with or without focal deficits or seizures with no evidence of re-bleeding in the presence of radiological vasospasm. Spinal MRI examinations were performed in all patients regardless of inpatient or outpatient status. If a vascular pathology was suspected, additional spinal DSA was performed. Complications such as re-bleeding, vasospasm, hydrocephalus, transient or permanent neurological deficits during the clinical course were recorded.

Statistical Analysis

All statistical analyses were conducted using SPSS for Windows version 15.0 (SPSS Inc. Chicago, IL, USA). A T-test was used to compare quantitative variants. A one-way ANOVA test was used to compare groups. Qualitative variants were compared using chi-square tests. $P < 0.05$ was considered statistically significant.

RESULTS

There were 41 men (51%) and 40 women (49%) with a mean age of 47.8 years (range 16 to 74 years). The majority of the patients (76 patients, 94%) had a World Federation of Neurosurgical Societies (WFNS) grade of I or II at admission. Fisher grade I or II SAH was encountered on the initial CT scans of 64 patients (79%). There were 33 patients (41%) with PM-SAH, 41 patients (51%) with nPM-SAH and 7 patients (8%) with CT negative-NNSAH. Statistically significant differences in Fisher grades were found between study groups at admission; however, no significant differences were found regarding WFNS grades.

Following the initial DSA, cranial MRI was performed on all patients within the first week after SAH. However, these investigations did not provide any additional information regarding the detection of the underlying cause in any of the three patient groups. Repeat DSA investigations were positive in 2 patients (2.5%), both from the nPM-SAH group (4.9%). The aneurysms, detected in the repeat DSA investigation, were as follows: a right distal superior cerebellar artery (dSCA) aneurysm and a dissecting right anterior cerebral artery (ACA) A1 segment aneurysm (Figures 1, 2). The patient with dSCA aneurysm underwent surgery and the aneurysm was clipped. Both surgical or endovascular treatment options were thought to have high risk for the patient with dissecting right A1 aneurysm. No intervention was performed, except shunt surgery for the hydrocephalus, for this particular patient and she had follow-up in the outpatient clinic. Spinal MRI was performed depending on the clinical course in patients with nPM-SAH prior to the repeat DSA regardless of inpatient or outpatient status. In the other 2 patient groups, spinal MRI was primarily used in the outpatients after the second DSA (2 weeks to 3 months after the SAH) unless the patient had unusual complaints such as back or neck pain. Spinal pathologies were found to be responsible for SAH in 3 patients (3.7%). Spinal MRI did not yield any abnormal findings in the CT-negative and PM-SAH groups. Namely, 2 spinal arteriovenous malformations (AVM) and a spinal intradural extramedullary tumor (schwannoma) were found in the nPM-SAH group (7.3%) (Figures 3, 4). The intradural extramedullary tumor was completely surgically removed. The other patients with cervical spinal AVMs underwent surgery

following endovascular treatment; the AVMs were completely removed.

Radiological vasospasm was detected in 16 patients (20%) (4 in the PM-SAH group and 12 in the nPM-SAH group) in the first or control DSA investigations. Clinical vasospasm causing transient neurological deficits was encountered in 10 patients (12%)(2 in the PM-SAH group and 8 in the nPM-SAH group). Early re-bleeding leading to neurological deterioration occurred in one patient (nPM-SAH group) who had a history of cocaine abuse. No statistically significant differences were found for these complications.

Hydrocephalus requiring external ventricular drainage (EVD) placement developed in 5 patients, and permanent CSF diversion with ventriculoperitoneal shunts was performed in only one of these cases (all in the nPM-SAH group). The patient who underwent shunt surgery had a partially thrombosed ACA A1 segment dissecting aneurysm. No statistically significant differences were found for hydrocephalus requiring EVD placement or shunt insertion.

The 75 patients with a Glasgow outcome scale (GOS) score of 5 were discharged from the hospital. The only permanent neurological deficits were abducens nerve palsy in one patient and mild hemiparesis in another patient. Both of these patients were in nPM-SAH group. The 5 patients with positive spinal MRI or repeat DSA, with detected underlying causes underwent surgery and/or endovascular treatment. Of these 5

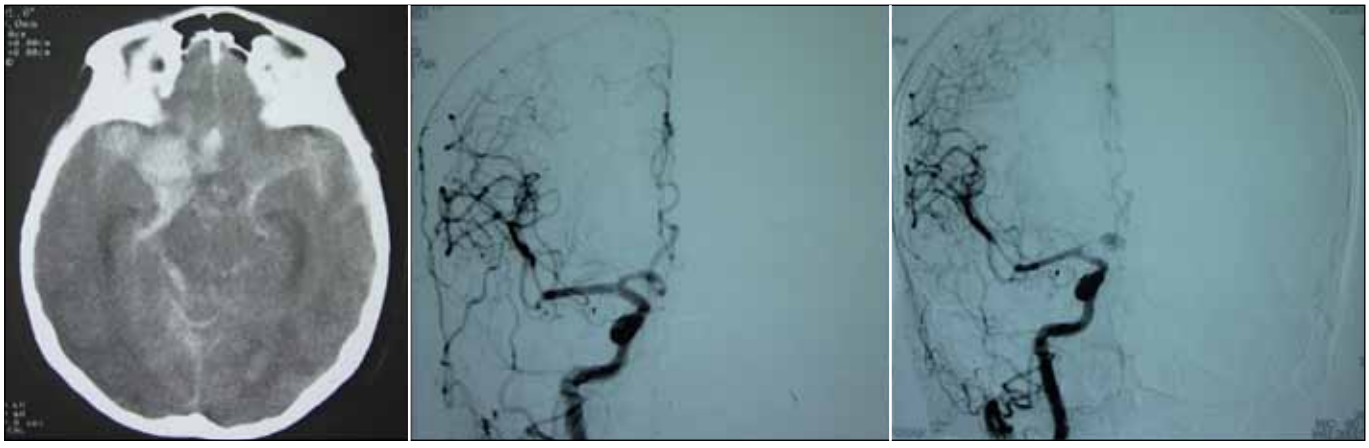

Figure 1: CT scan of a patient with NNSAH at admission revealed diffuse subarachnoid hemorrhage especially located on the right carotid cistern. The initial DSA was negative. On the repeat DSA investigation, right internal carotid artery injection showed a partially thrombosed, dissecting right A1 aneurysm.

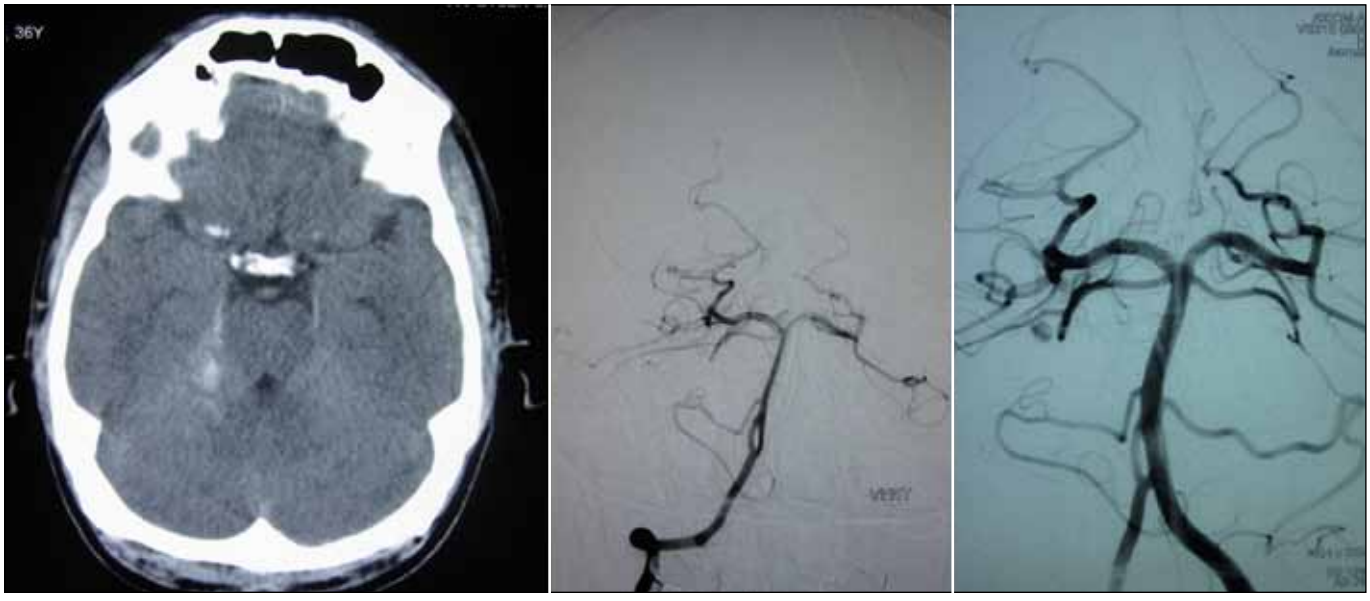

Figure 2: Admission CT scan of a patient revealed subarachnoid hemorrhage alongside the tentorium on right side (above left). Initial DSA investigation showed no aneurysm (above middle). Repeat DSA, however revealed a right superior cerebellar artery aneurysm. (above right).

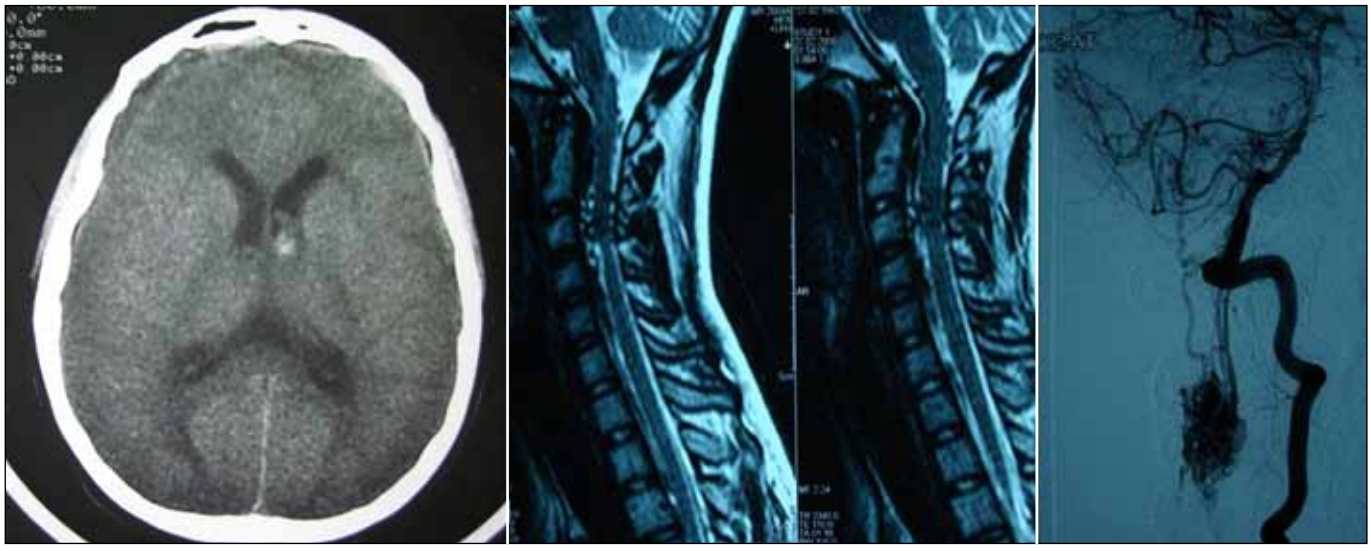

Figure 3: Initial CT scan of a patient revealed intraventricular subarachnoid hemorrhage (above left). Cervical MRI of the same patient revealed a suspicion of a vascular lesion (above middle). An arteriovenous malformation feeding from the vertebral arteries and draining towards the intracranial vessels between C2-C4 levels detected in vertebral injections (above right).

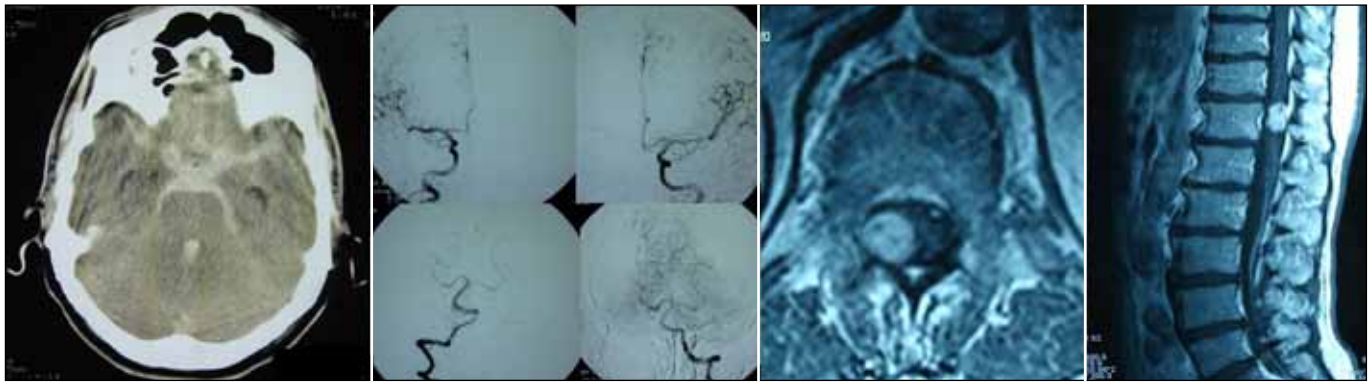

Figure 4: Initial CT scan of a patient showed diffuse subarachnoid hemorrhage (above left). Initial DSA revealed no abnormalities both in anterior and posterior circulation injections (above middle). Spinal MRI investigations in one patient revealed a 2.2x1.2x1 cm-sized mass-lesion located intradural extramedullary at Th 12 level, which was found to be responsible of SAH (above right).

patients, 2 were discharged with a GOS score of 2, two were discharged with a GOS score of 3 and one was discharged with a GOS score of 4. There was one death (1.2%) in our series. A 50-year-old female patient with an admission WFNS Grade of IV was lost due to severe cardiac failure and nosocomial pneumonia. The mean hospital stay was 10.9 days for the study cohort and, 6.3, 14.7 and 10.1 days for the study groups 1, 2 and 3, respectively. Statistically significant differences were found for the nPM-SAH group by means of hospital stay compared to the other two groups. Distributions of patients according to WFNS and Fisher grades, further radiological investigation results, complications and mean hospital stay are summarized in Table I. The results of statistical analyses are summarized in Table II.

■ DISCUSSION

After the first description by van Gijn et al. in 1985 (55), non-traumatic non-aneurysmal PM-SAH has been thoroughly investigated and defined as a benign form of SAH with relatively low morbidity and mortality rates (16,29,57). Lower complication risks, including vasospasm or hydrocephalus, have been reported especially for PM-SAH (47). The risk of re-bleeding is also reported to be minimal in PM-SAH (16,47). However, PM-SAH is not the only bleeding pattern in patients with NNSAH. A significant number of patients have different bleeding patterns on initial CT. Other bleeding patterns, such as sylvian, interhemispheric, intraventricular or convexal, may be categorized as nPM-SAH. The clinical course and complications of this subgroup have not been thoroughly studied, and controversial results have been reported. Besoglu et al. presented less favorable long-term clinical outcomes and quality of life scores for patients with nPM-SAH compared with those with PM-SAH (6). Andaluz and Zuccarello stated that nPM-SAH has a clinical course, complication rate and

outcome comparable to that of aneurysmal SAH (4). Andaluz and Zuccarello reported significantly longer intensive care and hospital stays, greater complication rates and poorer outcomes for nPM-SAH compared with PM-SAH. However, Gupta et al. reported similar outcomes for nPM-SAH if the patients with aneurysms detected on the repeat DSA investigations were excluded (23). Our results also support the benign nature of PM-SAH. Most complications were encountered in the nPM-SAH group. There were only four cases of radiological vasospasm and two cases of clinical vasospasm in the PM-SAH group. No complications were encountered in the CT-negative NNSAH. All of the other complications were encountered in the nPM-SAH group, including two minor permanent neurological deficits and one patient with hydrocephalus that required treatment with shunt surgery. The mean hospital stay was the shortest in the PM-SAH group (6.3 days), followed by the CT-negative NNSAH group (10.1 days). The mean hospital stay of the patients with nPM-SAH was significantly longer than that in the other two groups (14.7 days). The mortality rate was 1.2% in our series. That particular patient was in nPM-SAH group. Former studies reported significant mortality rates ranging from 3% to 12.8% for NNSAH (4,22,54). We postulated that the lower mortality rate in our series was associated with better patient WFNS and Fisher grades at admission.

Patients with NNSAH tend to be male, younger and less hypertensive compared with those with aneurysmal SAH according to the current literature (6,13,23,42,52). The age-related epidemiological data of our study cohort was in line with that of existing literature (mean age of 51 years); however, our study found no gender predominancy (51% to 49%). A female predominancy (59%) was found in nPM-SAH group, whereas a male predominancy (64%) was found in PM-SAH group. The overall mortality and morbidity rates in our study group appear to be considerably lower than those for aneurysmal SAH. However, a clinical deterioration (due to ventricular dilation and/or clinical vasospasm) was noted in 13 of 81 patients (16%) during hospitalization. Two of these patients were in the PM-SAH group (6%), and 11 patients were in the nPM-SAH group (27%). In light of these results, nPM-SAH may show a clinical course more similar to aneurysmal SAH than NNSAH. Clinical worsening in patients with PM-SAH and especially nPM-SAH in our study group created doubts regarding the benign

Table I: Summary of Clinical Features and Complications

	Total	PM-SAH	nPM-SAH	CT (-)-SAH
Patient number by bleeding pattern	81	33 (41%)	41 (51%)	7 (8%)
Fisher Grade				
Grade I	7 (8.6%)	0 (0%)	0 (0%)	7 (100%)
Grade II	57 (70%)	30 (91%)	27 (66%)	0 (0 %)
Grade III	11 (14%)	3 (9%)	8 (20%)	0 (0 %)
Grade IV	6 (7.4%)	0 (0 %)	6 (15 %)	0 (0 %)
WFNS Grade				
Grade I	66 (82%)	31 (94%)	28 (68%)	7 (100%)
Grade II	10 (12%)	2 (6%)	8 (20%)	0 (0 %)
Grade III	2 (2.5%)	0 (0%)	2 (4.9%)	0 (0 %)
Grade IV	1 (1.2%)	0 (0%)	1 (2.4%)	0 (0 %)
Grade V	2 (2.5%)	0 (0%)	2 (4.9%)	0 (0%)
Imaging modalities for further investigation				
Repeat DSA (+)	2 (2.5%)	0 (0%)	2 (4.9%)	0 (0 %)
Cranial MRI (+)	0 (0 %)	0 (0 %)	0 (0%)	0 (0 %)
Spinal MRI (+)	3 (3.7%)	0 (0%)	3 (7.3%)	0 (0 %)
Complications				
Radiologic VS	16 (20%)	4 (12%)	12 (29%)	0 (0 %)
Clinic VS	10 (12%)	2 (6%)	8 (20%)	0 (0 %)
Early re-bleeding	1 (1.2%)	0 (0 %)	1 (2.4%)	0 (0 %)
EVD placement	5 (6.2%)	0 (0 %)	5 (12%)	0 (0 %)
VP Shunt	1 (1.2%)	0 (0 %)	1 (2.4%)	0 (0 %)
Permanent deficit	2 (2.5%)	0 (0 %)	2 (4.9%)	0 (0 %)
Mean hospital stay	10.9 days	6.3 days	14.7 days	10.1 days

nature of NNSAH. Although the source of bleeding could not be demonstrated, NNSAH is a variant of SAH and should not be underestimated. As our results indicate, any complications related to SAH may also occur in this clinical setting. Bleeding and coagulation disorders or anti-thrombotic drug usage is a known cause of NNSAH. Relative poorer outcomes were associated with above mentioned circumstances (26). Hui et al. reported poorer outcomes and diffuse bleeding patterns in patients with NNSAH under anti-thrombotic drug usage (27). Patients with anti-thrombotic drug usage and/or bleeding and coagulation disorders may also carry a higher risk of clinical worsening. Therefore, shortening the hospital stay or early discharge should be avoided, especially in nPM-SAH.

In order to understand the clinical course of different subtypes of NNSAH, we also conducted a contemporary literature review to compare published series. We did a MEDLINE search using terms "non-aneurysmal subarachnoid hemorrhage" or "non-perimesencephalic subarachnoid hemorrhage" or "perimesencephalic subarachnoid hemorrhage" or "pretruncal" and included 31 studies in English language published between the years 2000 and 2015, which attempted to compare different subtypes of NNSAH according to the bleeding pattern on the initial CT scan (2,4,6-8,10,11,14,15,17,22,23,26-28,30,32,35-41,43-45,51,53,58,59). Subtypes were classified as they were classified in our series (PM- ,nPM-, CT(-)-SAH). Other subtypes such as convexal, sylvian, diffuse in other studies were labelled under nPM-SAH in our review. Clinical features and complications of these 31 series and the current cohort were summarized in Table III and IV (Note that Table IV only contains 25 studies, because 6 studies did not provide any data for complications). As the results demonstrate, there is a great variety for complication rates, length of hospital stay, mortality-morbidity rates and even gender predominancy or mean age in different studies. For example, hospital stays show a large range from 7.6 days to 21 days. Similarly, deficits and mortality rates vary greatly from 0 to 30% and from 0 to 12.8% respectively. Most studies provide only limited data as seen on the Tables III and IV. We think, that our cohort contains important details about the clinical course, possible complications as well as further investigation protocols. As our literature review indicates, there is no consensus about the clinical course and possible complications of NNSAH, as it is for the further investigation protocols. We think, our series could provide an insight to other institutions in order to make some modifications of their patient management.

Due to the benign course as well as lower mortality and morbidity rates of NNSAH, some authors recommended no further DSA investigations for patients with initial negative angiograms (50,56). However, in 2 to 21% of NNSAH cases, additional information may be provided via repeat DSA investigations to determine the source of bleeding (4,31,49,57). Some authors even advocated a third or fourth DSA (4). Repeat DSA investigations were positive in two patients (2.5%) in our study group. The aneurysms were detected both in patients with nPM-SAH (4.9%). Initial DSA may yield false negative results due to a variety of conditions, including vasospasm, mass effect caused by hematoma, thrombosis or technical issues (33,53). No bleeding source was detected in the control DSA investigations of the CT-negative NNSAH group. We assert that control DSA can play a crucial role in the management of nPM-SAH. All patients with nPM-SAH should undergo a repeat DSA to determine the underlying cause. A third DSA in this series was only used in one patient with early re-bleeding and was negative in this particular case. A third or even fourth DSA may be indicated according to the clinical course of the patient or due to other suspected conditions.

Cranial MRI was performed in all patients as the third imaging modality (after CT and DSA) within the first week following the SAH. The rationale behind using MRI in NNSAH was to exclude small volume vascular malformations. However, no additional data were provided by this investigation, and small volume vascular malformations were absent from our patient group. Interestingly, our results are in accordance with the current literature (4,41,53). Topcuoglu et al. performed cranial MRI in 57% of their study group of 86 patients with no positive results (53). They suggested that MRI is more useful in revealing vascular insults and strokes related to vasospasm. Andaluz and Zuccarello performed cranial MRI on 92 patients with NNSAH in a study to assess the diagnostic yield of additional neuroimaging modalities (4). As in our series, they also obtained 100% negative results.

Spinal MRI was performed in all patients as the fourth neuroimaging tool. The rationale behind the use of spinal MRI is the lack of data in the current literature regarding the role of spinal pathologies in NNSAH. The detection of a spinal tumor or vascular malformation, which may be an underlying cause of NNSAH, has been reported previously in sporadic cases (1,4,5,9,25,40,54), and the role of spinal MRI as a diagnostic tool for NNSAH etiology has not been investigated in a clinical study. Previous clinical studies have reported incidences of

Table II: Summary of Statistical Analyses of the Study. There were Significant Differences in Fisher Grades at the Admission CT-Scans and Mean Hospital Stays in Favour of the PM-SAH Group. (Marked)

	p value
Fisher Grade	**<0.001***
WFNS Grade	0.244
Repeat DSA (+)	0.368
Cranial MRI (+)	1.000
Spinal MRI (+)	0.219
Radiologic VS	0.071
Clinic VS	0.126
Early re-bleeding	0.610
EVD placement	0.074
VP Shunt	0.610
Permanent deficit	0.368
Mean hospital stay	**<0.001***

Table III: Comparison of the 31 Series of NNSAH Published Between 2000 and 2015 and the Current Series by Means of Patient Demographics, Study Design and Lenght of Hospital Stay (n: none, nA: not available)

Study Author/Year/Ref.		No. of Patients (PM/nPM/CT(-))	Mean Age (PM/nPM/CT(-))	Gender (M%) (PM/nPM/CT(-))	Hospital stay (days) (PM/nPM/CT(-))
Agid et al, 2010 [2]	Retrospective	193 (93/68/32)	51.6 (nA)	60.6 (62/57/63)	nA
Andaluz et al, 2008 [4]	Retrospective	92 (45/47/0)	49.4 (48/50.8/n)	34 (33/34/n)	6.3 (4.3/8.3/n)
Besoglu et al, 2010 [6]	Retrospective	26 (12/14/0)	58.5 (54/63/n)	65 (75/57/n)	16.5 (11.2/21/n)
Boswell et al, 2013 [7]	Retrospective	30 (14/16/0)	56.3 (nA)	57 (nA)	12.9 (12.5/13.2/n)
Caeiro et al, 2011 [8]	Prospective	47 (10/37/0)	53.5** (nA)	43 (40/43/n)	nA
Canneti et al, 2015 [10]	Retrospective	41 (17/24/0)	55 (52/57/0)	51 (53/50/n)	21 (17/24/0)
Canovas et al, 2012 [11]	Retrospective	108 (68/40/0)	52.4 (50.4/55/n)	45 (48/41/n)	nA
Delgado Almandoz et al, 2012 [14]	Prospective	72 (29/39/4)	53.1 (nA)	36 (41/33/25)	nA
Delgado Almandoz et al, 2014 [15]	Retrospective	39 (12/27/0)	55.5 (nA)	59 (58/59/n)	13.2 (nA)
Fontonella et al, 2011 [17]	Retrospective	102 (23/79/0)	55 (54/55/n)	58 (70/56/n)	nA
Gross et al, 2012 [22]	Retrospective	77 (31/44/2)	59.8 (nA)	48 (nA)	nA
Gupta et al, 2009 [23]	Prospective	52 (18/34/0)	44.7 (48.3/42.8/n)	67 (78/62/n)	nA
Hui et al, 2009 [26]	Retrospective	94 (31/63/0)	nA	61 (nA)	nA
Hui et al, 2011 [27]	Retrospective	236 (79/157/0)	51 (nA)	48 (nA)	nA
Hui et al, 2012 [28]	Retrospective	83 (19/64/0)	50 (nA)	48 (nA)	nA
Ildan et al, 2002 [30]	Retrospective	84 (29/30/25)	nA	nA	nA
Jung et al, 2006 [32]	Retrospective	143 (94/37/12)	52.3 (nA)	42 (nA)	nA
Kang et al, 2009 [35]	Retrospective	52 (23/29/0)	55.4 (54/56/n)	54 (65/45)	nA
Kawamura et al, 2011 [36]	Retrospective	13 (10/3/0)	59.5 (62/52)	62 (60/66)	nA
Kelliny et al, 2011 [37]	Retrospective	78 (19/37/16)	nA	nA	10 (5/14/4)
Khan AA et al, 2013 [38]	Retrospective	50 (17/23/10)	52.5 (49/56/52)	60 (71/61/40)	8.4 (8.3/10/5)
Lin et al, 2012 [39]	Retrospective	68 (27/39/2)	59.5 (nA)	51.5 (nA)	nA
Little et al, 2007 [40]	Retrospective	100 (16/69/15)	48 (50/48/42)	36 (56/32/33)	10 (9/11/6)
Maslehaty et al, 2011 [41]	Retrospective	179 (47/132/n)	nA	nA	nA
Miranpuri et al, 2013 [43]	Retrospective	46 (32/14/0)	57.3 (55.8/60.7/n)	54 (59/42/n)	nA
Moscovici et al, 2013 [44]	Retrospective	56 (25/31/0)	53.7 (49.3/57.4/n	54 (56/52/n)	7.6 (5.2/9.6/n)
Muroi et al, 2011 [45]	Prospective	20 (11/9/0)	56.6 (nA)	65 (nA)	nA (10/16/n)*
Ruigrok et al,2002 [51]	Retrospective	88 (73/15/0)	53 (53/53/n)	59 (57/67/n)	nA
Topcuoglu et al, 2003 [53]	Retrospective	86 (36/41/9)	54 (54/58/39)	58 (61/51/78)	13.3 (11/16.8/7)
Yap et al, 2015 [58]	Retrospective	114 (41/56/17)	nA	nA	nA
Zhong et al, 2014 [59]	Retrospective	83 (49/34/0)	53.4 (54/53/n)	51 (49/53)	nA
Current Study	Retrospective	81 (33/41/7)	47.8 (49/46.3/43.3)	51 (64/41/43)	10.9 (6.3/14.7/10.1)

Table IV: Rates of Complications and Mortality of 25 Studies of NNSAH Published between 2000 and 2015 and the Current Cohort were Summarized in Table

Study Author/Year/Ref.	Radiologic VS (%) (PM/nPM/CT(-))	Clinical VS (%) (PM/nPM/CT(-))	Radiologic HS (%) (PM/nPM/CT(-))	EVD placement (%) (PM/nPM/CT(-))	VP Shunt (%) PM/nPM/CT(-)	Deficit (%) (PM/nPM/CT(-))	Rebleeding (%) (PM/nPM/CT(-))	Mortality
Andaluz et al, 2008 [4]	14 (7-21-n)	11 (2-19-n)	15 (4-26-n)	14 (4-26-n)	2 (0/4/n)	12 (0-23-n)	5 (2-9-n)	12.8%
Besoglu et al, 2010 [6]	4 (0-7-n)	0	nA	nA	12 (0/21/n)	30 (16-43-n)	0	4%
Boswell et al, 2013 [7]	13 (0-25-n)	0	47 (50-44-n)	30 (29-31-n)	3 (0/6/n)	0	3 (0-6-n)	0%
Caeiro et al, 2011 [8]	nA	15 (20-14-n)	45 (20-51-n)	nA	nA	nA	nA	0%
Canneti et al, 2015 [10]	9.8 (7-12.5-n)	nA	29 (23-33-n)	17 (0-29-n)	0	2 (0-4-n)	2 (0-4-n)	0%
Canovas et al, 2012 [11]	nA	2 (0-4-n)	nA	nA	6 (2/10/n)	1 (0-2-n)	0	0%
Delgado Almandoz et al, 2012 [14]	38 (45-33-25)	3 (0-5-0)	nA	25 (10-38-0)	10 (0/18/0)	nA	nA	nA
Fontonella et al, 2011 [17]	8 (4-11-n)	3 (4-3-n)	6 (0/10/n)	nA	2 (0/3/n)	2 (0-3-n)	4 (0-5-n)	4%
Gross et al, 2012 [22]	26 (16-39-0)	nA	nA	nA	nA	4 (0-8-nA)	nA	1%
Gupta et al, 2009 [23]	nA	nA	nA	nA	nA	21 (11-26-n)	nA	0%
Hui et al, 2009 [26]	nA	22 (10-29-n)	37 (10-51-n)	31 (10-41-n)	15 (3/21/n)	12 (3-24-n)	1 (3-0-n)	5%
Hui et al, 2011 [27]	nA	6 (nA)	nA	27 (nA)	8 (nA)	18 (9-23-n)	nA	6%
Hui et al, 2012 [28]	nA	6 (nA)	nA	nA	4 (nA)	16 (nA)	nA	8%
Ildan et al, 2002 [30]	nA	nA	5 (11/3/0)	nA	4.7 (11/3/0)	13 (7-23-4)	7 (7-3-11)	8.3%
Jung et al, 2006 [32]	nA	nA (14/22/0)	10 (11/8/0)	nA	nA	8 (7-14-nA)	2 (1-5-0)	0%
Kang et al, 2009 [35]	15 (0-28-n)	0	25 (9-38-n)	0	6 (0/10/n)	10 (4-14-n)	2 (0-3-n)	0%
Kawamura et al, 2011 [36]	0	0	8 (nA)	nA	8 (nA)	8 (nA)	nA	0%
Khan AA et al, 2013 [38]	nA	4 (0/9/0)	nA	16 (6-30-0)	2 (0/4/0)	6 (0-13-0)	0	0%
Lin et al, 2012 [39]	nA	15 (4-23-0)	nA	38 (nA)	19 (4/31/0)	27 (nA)	0	1%
Little et al, 2007 [40]	nA	nA	33 (0/48/0)	nA	nA	27 (nA)	0	0%
Maslehaty et al, 2011 [41]	nA	nA	nA	nA	nA	nA	nA	7%
Moscovici et al, 2013 [44]	25 (0-45-n)	23 (0-46-n)	27 (0-48-n)	14 (0-26-n)	5 (0-10-n)	12.5 (0-22-n)	2 (0-3-n)	0%
Muroi et al, 2011 [45]	nA	10 (0-22-n)	nA	nA	nA	5 (nA)	nA	nA
Topcuoglu et al, 2003 [53]	26 (25-27-3)	6 (0-12-0)	nA	nA	nA	nA	nA	nA
Zhong et al, 2014 [59]	nA	6 (2-15-n)	nA	nA	7.2 (2/14.7/n)	4 (0-8-n)	5 (0-12-n)	1.2%
Current Study	19.7 (12-29-0)	12.3 (6-19.5-0)	11.1 (3-17-14)	6.2 (0/12.2/0)	1.2 (0/2.4/0)	2.5 (0/4.9/0)	1.2 (0/2.4/0)	1.2%

VS: *vasospasm,* ***HS:*** *Hydrocephalus,* ***EVD:*** *External ventricular drainage,* ***VP:*** *ventriculoperitoneal,* ***n:*** *none,* ***nA:*** *not available.*

1% to 3% in spinal pathologies responsible for NNSAH (4,54). However, spinal MRI was primarily performed in patients who had signs or symptoms of spinal pathologies. Therefore, only a small number of the patients underwent spinal MRI in these series. Little et al. performed cervical MRI in 84 patients and detected only one vascular malformation (1%) (40). Maslehaty et al. performed MRI to the craniocervical region in all of 179 patients with NNSAH and obtained 100% negative results (41). Germans et al. performed MRI of the entire spinal neuraxis in 42 of 47 patients with nPM-SAH and found a 9% incidence of spinal pathologies in this subgroup (18). The same group performed spinal MRI in 51 patients with PM-SAH in their later publication and found 100% negative results (19). They found only 2% positive results in the spinal MRI of 37 patients with nPM-SAH in the same study. In their latest publication on the subject, they concluded that the diagnostic yield and relevance of spinal MRI is also low for the patients with nPM-SAH (4%) (2). Spinal MRI has been used at our institution on a routine basis in the clinical work-up of patients with NNSAH. We found an overall incidence of 3.7% for spinal pathologies in patients with NNSAH. All these cases were encountered in nPM-SAH group with an 7.3% incidence for this subgroup. Our incidence is relatively higher compared to the series by Germans et al. (18-20). We think that spinal MRI is of the utmost importance in the diagnostic work-up of nonaneurysmal SAH especially in patients with nPM-SAH. Based on the CT findings of our three cases, we think that the presence of intraventricular blood, particularly within the fourth ventricle may be associated with a spinal pathology as the underlying cause. However, the number of cases is not sufficient to draw definitive conclusions on the CT findings which may be highly suggestive of a spinal bleeding source.

Although numerous studies have been made, diagnostic algorithm for NNSAH still remains unclear. A recent meta-analysis by Kalra et al. (34) reported strong evidence that in PM-SAH there is no foundation for further investigations. Our study also provided similar additional data. However, with applying this strategy on all patients with NNSAH, a small amount of cases with undefined underlying cause may be missed. Therefore, we suggest our diagnostic work-up for patients with nPM-SAH, namely repeat DSA and spinal MRI, until an evidence-based guideline is established for the management of NNSAH.

The present study has some limitations. First, the sample size in this study is a moderate one. Even though it is larger than most of the studies referenced in this report on the subject, it is not large enough to draw definitive conclusions on further investigation protocols. Second, the study is a retrospective study, which reviewed the further diagnostic work-up and clinical course for different types of NNSAH. However, important aspects such as long term outcome, cognitive impairment or psychiatric disorders remained unreviewed. Third, today CT-angiography (CTA) is the first investigation in most neurosurgical units. However, DSA was the first investigation following the initial CT in our institution without the use CTA. Therefore, we could not comment about the diagnostic value of DSA compared to CTA. Fourth, xanthochromia of the CSF was only assessed with visual inspection of the supernatant in the seven patients with negative initial CT-scan. Recent publications underlined the importance of the utility of spectrophotometry, bilirubin and oxyhaemoglobin determination, CSF cytology and ferritin measurement for more reliable detection of the xanthochromia (46). According to the national guidelines spectrophotometry is routinely used in United Kingdom, whereas its usage varies in the rest of Europe and it is not used in North America (12). A recent systematic review reported that it is not possible to provide a definitive conclusion about the diagnostic accuracy of spectrophotometry versus visual inspection (12). A recent study by Hann et al. suggested the combined use of both methods in order to achieve higher diagnostic accuracy (24). The use of visual inspection alone, which is criticised as being unreliable and subjective method for the detection of xanthochromia, is one weakness of the current study. Lastly, like most of the single center studies, there might be a selection bias or sample bias.

■ CONCLUSION

Our series demonstrate that NNSAH has a favorable clinical outcome compared with aneurysmal SAH. PM-SAH has a better clinical course, better clinical outcomes and lower complication rates compared with nPM-SAH. During the clinical course, neurological deterioration due to significant complications may occur, especially in nPM-SAH. Therefore, hospital stay shortening or early discharge due to the benign nature of the disease should be avoided in nPM-SAH. Repeat DSA investigations should be performed on each patient with nPM-SAH to exclude aneurysmal SAH. Cranial MRI did not provide additional data for the detection of the underlying cause (100% negative). Spinal MRI detected spinal pathologies in 3 cases (7.3%) with nPM-SAH. We assert that spinal MRI may provide valuable information regarding the bleeding source and should be considered in the diagnostic work-up for these patients.

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