

Epidemiological Features of Nontraumatic Spontaneous Subarachnoid Hemorrhage in China: A Nationwide Hospital-based Multicenter Study

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Abstract

Background: Nontraumatic spontaneous subarachnoid hemorrhage (SAH) is associated with a high mortality. This study was conducted to investigate the epidemiological features of nontraumatic spontaneous SAH in China.

Methods: From January 2006 to December 2008, the clinical data of patients with nontraumatic SAH from 32 major neurosurgical centers of China were evaluated. Emergent digital subtraction angiography (DSA) was performed for the diagnosis of SAH sources in the acute stage of SAH (≤ 3 days). The results and complications of emergent DSA were analyzed. Repeated DSA or computed tomography angiography (CTA) was suggested 2 weeks later if initial angiographic result was negative.

Results: A total of 2562 patients were enrolled, including 81.4% of aneurysmal SAH and 18.6% of nonaneurysmal SAH. The total complication rate of emergent DSA was 3.9% without any mortality. Among the patients with aneurysmal SAH, 321 cases (15.4%) had multiple aneurysms, and a total of 2435 aneurysms were detected. The aneurysms mostly originated from the anterior communicating artery (30.1%), posterior communicating artery (28.7%), and middle cerebral artery (15.9%). Among the nonaneurysmal SAH cases, 76.5% ($n = 365$) had negative initial DSA, including 62 cases with peri-mesencephalic nonaneurysmal SAH (PNSAH). Repeated DSA or CTA was performed in 252 patients with negative initial DSA, including 45 PNSAH cases. Among them, the repeated angiographic results remained negative in 45 PNSAH cases, but 28 (13.5%) intracranial aneurysms were detected in the remaining 207 cases. In addition, brain arteriovenous malformation (AVM, 7.5%), Moyamoya disease (7.3%), stenosis or sclerosis of the cerebral artery (2.7%), and dural arteriovenous fistula or carotid cavernous fistula (2.3%) were the major causes of nonaneurysmal SAH.

Conclusions: DSA can be performed safely for pathological diagnosis in the acute stage of SAH. Ruptured intracranial aneurysms, AVM, and Moyamoya disease are the major causes of SAH detected by emergent DSA in China.

Key words: Arteriovenous Malformation; Epidemiology; Intracranial Aneurysm; Moyamoya Disease; Subarachnoid Hemorrhage

INTRODUCTION

Nontraumatic spontaneous subarachnoid hemorrhage (SAH) is a neurologic emergency comprising 1–7% of all strokes, and the risks of morbidity and mortality associated with SAH are very high.^[1] According to the WHO MONICA stroke study, the overall 28-day case fatality rate after SAH ictus was 41.7%.^[2] As many as 46% of SAH survivors may have long-term cognitive impairment affecting functional status and quality of life due to symptomatic vasospasm.^[3,4] Different sources of SAH may result in different outcomes, and the early diagnosis and management of SAH is now highly recommended by guidelines.^[5] Therefore, we have to assess

the safety and efficiency of emergent cerebral angiography for pathological diagnosis and understand the epidemiologic features of SAH in Chinese population. In this article, we report the results of a large multicenter epidemiology survey

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of nontraumatic SAH in China using cerebral angiography within the acute stages (≤ 3 days) of SAH.

METHODS

This study was approved by Huashan Hospital Institutional Review Board, Fudan University, Shanghai, China. From January 2006 to December 2008, 32 major neurosurgical centers in China participated in this prospective observational survey. SAH was diagnosed by computed tomographic (CT) scan or lumbar puncture that was positive for xanthochromia in suspected cases. Patients aged <18 years or >80 years, or having a history of head trauma, were excluded from the study. Finally, a prospective database of patients with nontraumatic spontaneous SAH was established.

The pathological sources of SAH were evaluated by conventional catheter-based cerebral digital subtraction angiography (DSA) in the acute stages (≤ 3 days) of SAH. Standard angiographic views with/without supplementary oblique views were obtained through both internal or external carotid arteries and vertebral arteries. Rotational angiography and three-dimensional reconstruction were conducted for the clear identification of suspected hemorrhagic sources. If specific source of SAH was detected, it was called positive angiogram, otherwise it would be called negative angiogram. For those cases with negative initial angiogram in the acute stage of SAH, a repeat of DSA or CT angiography (CTA) was suggested 2 weeks later [Figure 1].

Basic clinical data including patients' sex, age, smoking and drinking history, personal and family history, diabetes, hypertension, dyslipidemia, cause of bleeding, and drug use were collected. SAH was graded according to the modified Fisher scale that was based on hemorrhage pattern on admission CT.^[6] Neurologic functional status on admission was evaluated using Hunt–Hess scale.^[7,8] The results and complications of DSA were analyzed, and different angiographic results of SAH were recorded.

Statistical analysis was carried out using software SPSS 22.0 (IBM, USA). For comparisons of baseline characteristics

between cohorts, Fisher's exact test and Chi-square test for categorical data and independent Student's *t*-test for continuous data were used. The statistical difference was considered as $P < 0.05$.

RESULTS

A total of 2562 patients with nontraumatic spontaneous SAH were included in the survey. All SAH cases were revealed by CT or lumbar puncture, and hemorrhagic sources were identified by DSA in acute stages of SAH. The total complication rate of emergent DSA was 3.9% without any mortality, including 10 cases (0.4%) of rebleeding and 91 cases (3.5%) of cerebral vasospasm during DSA procedure.

Clinical characteristics of all SAH patients were summarized in Table 1. A total of 2085 (81.4%) cases with SAH were attributed to the rupture of intracranial aneurysms, while the other 477 (18.6%) cases were caused by other reasons. Patients with aneurysmal SAH were slightly older than those with nonaneurysmal SAH (51.8 ± 10.7 years vs. 49.5 ± 12.3 , $P < 0.001$). Although more male patients with SAH were observed in this study, overall, aneurysmal SAH tended to occur more in female patients than nonaneurysmal SAH (48.7% vs. 42.3%, $P = 0.012$). There were no significant differences in smoking and drinking history, family history of cerebrovascular diseases, diabetes, or dyslipidemia between the aneurysmal SAH and nonaneurysmal SAH groups. However, more cases with hypertension were observed in the aneurysmal SAH group compared with the nonaneurysmal SAH group (30.8% vs. 17.8%, $P < 0.001$). About 260 (12.5%) patients in the aneurysmal SAH group had a history of previous rupture. The stimulation of hemorrhage was similar in both groups, except that more nonaneurysmal SAH might be associated with emotional excitement than aneurysmal SAH (13.0% vs. 9.0%, $P = 0.007$). The severity of SAH was worse in the aneurysmal SAH group because more cases with high modified Fisher scores were detected ($P < 0.001$). Therefore, state of consciousness and neurological function after SAH seemed to be better in the nonaneurysmal SAH group ($P = 0.001$) as evidenced by more cases having low Hunt–Hess scores.

Among the aneurysmal SAH patients, 321 cases (15.4%) had multiple aneurysms, and a total of 2435 aneurysms were detected. The distribution of all aneurysms is listed in Table 2. Anterior communicating artery (ACoM) aneurysms (30.1%, $n = 734$), posterior communicating artery (PCoM) aneurysms (28.7%, $n = 700$), and middle cerebral artery (MCA) aneurysms (15.9%, $n = 386$) were the most common aneurysms detected in this study.

The distribution of nonaneurysmal SAH sources is summarized in Table 3. Nearly 76.5% ($n = 365$) had negative initial DSA with uncertain sources of bleeding. Among them, the pattern of peri-mesencephalic nonaneurysmal SAH (PNSAH) was detected in 62 cases (13.0% of all nonaneurysmal SAH). However, only 252 cases with negative initial angiogram, including 45 cases of

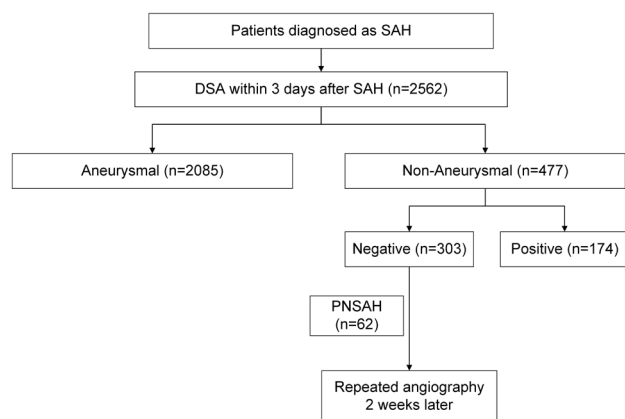


Figure 1: The flow diagram of the study. SAH: Subarachnoid hemorrhage; DSA: Digital subtraction angiography; PNSAH: Peri-mesencephalic nonaneurysmal SAH.

Table 1: Clinical characteristics of subarachnoid hemorrhage patients in 32 centers

Characteristics	Aneurysmal SAH, <i>n</i> = 2085	Nonaneurysmal SAH, <i>n</i> = 477	<i>P</i>
Age (years)	51.8 ± 10.7	49.5 ± 12.3	<0.001
Male:female	1069 (51.3):1016 (48.7)	275 (57.7):202 (42.3)	0.012
Smoking history	342 (16.4)	102 (21.4)	0.010
Moderate and heavy drinking	241 (11.6)	67 (14.0)	0.132
Family history			
Cerebral aneurysm	6 (0.3)	2 (0.4)	0.642
Polycystic kidney	2 (0.1)	–	0.499
Irrelevant intracranial hemorrhage	4 (0.2)	2 (0.4)	0.354
Diabetes	64 (3.1)	8 (1.7)	0.097
Hypertension	642 (30.8)	85 (17.8)	<0.001
Dyslipidemia	22 (1.1)	6 (1.3)	0.701
Cause of bleeding			
Coughing, breath holding, or straining at stool	154 (7.4)	42 (8.8)	0.293
Emotional excitement	187 (9.0)	62 (13.0)	0.007
Physical activity	126 (6.0)	26 (5.5)	0.621
Drinking	7 (0.3)	2 (0.4)	0.781
Sexual intercourse	5 (0.2)	1 (0.2)	0.902
Bathing	15 (0.7)	2 (0.4)	0.466
Others	11 (0.5)	5 (1.0)	0.193
Modified Fisher score			
0–2:3–4	1346 (64.6):739 (35.4)	404 (85.7):73 (15.3)	<0.001
Hunt and Hess score			
1–3:4–5	1931 (92.6):154 (7.4)	461 (96.6):16 (3.4)	0.001

Data were presented as *n* (%) or mean ± SD. SD: Standard deviation; SAH: Subarachnoid hemorrhage.

Table 2: Distribution of aneurysms among the aneurysmal subarachnoid hemorrhage patients

Location	<i>n</i> (%)
AComA AN	734 (30.1)
PComA AN	700 (28.7)
MCA AN	386 (15.9)
OA AN	100 (4.1)
ACA AN	92 (3.8)
VA AN	55 (2.3)
BA AN	50 (2.1)
PCA AN	48 (2.0)
ICA bifurcation AN	47 (1.9)
PICA AN	44 (1.8)
ICA clinoid AN	31 (1.3)
AchoA AN	30 (1.2)
SCA AN	14 (0.6)
ICA-CS AN	15 (0.6)
AICA AN	11 (0.5)
SHA AN	6 (0.2)
Others	72 (3.0)
Total	2435 (100)

AComA AN: Anterior communicating artery aneurysm; PComA AN: Posterior communicating artery aneurysm; MCA AN: Middle cerebral artery aneurysm; OA AN: Ophthalmic artery aneurysm; ACA AN: Anterior cerebral artery aneurysm; VAAN: Vertebral artery aneurysm; BAAN: Basilar artery aneurysm; PCA AN: Posterior cerebral artery aneurysm; ICA bifurcation AN: Internal carotid artery bifurcation aneurysm; PICA AN: Posterior inferior cerebellar artery aneurysm; ICA clinoid AN: Internal carotid artery aneurysms in the clinoid segment; AchoAAN: Anterior choroidal artery aneurysm; SCAAN: Superior cerebellar artery aneurysm; ICA-CS AN: Internal carotid arterial aneurysms in the cavernous segment; AICA AN: Anterior inferior cerebellar artery aneurysm; SHA AN: Superior hypophyseal artery aneurysm.

PNSAH, accepted repeated DSA or CTA examination. The repeated angiographic result remained negative in 45 PNSAH cases, but 28 (13.5%) intracranial aneurysms were detected in the remaining 207 cases. On the contrary, in cases with positive DSA findings, brain arteriovenous malformation (AVM) (7.5%, *n* = 36), Moyamoya disease (7.3%, *n* = 35), stenosis or sclerosis of the cerebral artery (2.7%, *n* = 13), and dural arteriovenous fistula or carotid cavernous fistula (2.3%, *n* = 11) were the major specific causes of nonaneurysmal SAH.

DISCUSSION

Previously, epidemiological studies revealed that SAH has a steady increase in incidence in the Chinese population.^[9-12] The development of both diagnostic modalities and emergent rescuing capabilities is the most important contributor to this discrepancy. This study is based on nationwide data collected from 32 major neurosurgical centers and represents the largest hospital-based epidemiological analysis of SAH in China. We evaluated the effectiveness and safety of emergent DSA for the pathogenic diagnosis of SAH and depicted the etiological distribution of aneurysmal and nonaneurysmal SAH.

Undoubtedly, DSA is highly recommended as the primary method to elucidate the cause of SAH.^[5] Due to the rapid development of neurosurgery in many hospitals in China, the emergent DSA for SAH patients was available almost at a nationwide level. The total complication rate of DSA in the acute stage of SAH in our cohort was limited to a satisfactory

Table 3: Etiology distribution of nonaneurysmal subarachnoid hemorrhage patients

Diagnosis	n (%)
PNSAH	62 (13.0)
AVM	36 (7.5)
Moyamoya or Moyamoya syndrome	35 (7.3)
Stenosis or sclerosis of cerebral artery	13 (2.7)
DAVF or CCF	11 (2.3)
Brain tumor apoplexy	6 (1.3)
Cerebral vasculitis	3 (0.6)
Venous sinus thrombus	2 (0.4)
Other cerebral vasculopathy	6 (1.3)
Uncertain causes (PNSAH not included)	303 (63.5)
Total, n	477

PNSAH: Peri-mesencephalic nonaneurysmal subarachnoid hemorrhage; AVM: Arteriovenous malformation; DAVF: Dural arteriovenous fistula; CCF: Carotid cavernous fistula; SAH: Subarachnoid hemorrhage.

level (3.9%) without any death; however, it seems to be slightly higher compared with previous studies.^[13,14] The reason may be that SAH itself is an independent risk factor of the DSA procedure and emergent DSA was performed just within 3 days after SAH ictus in our study.^[13,14] Also unsurprisingly, vasospasm was the primary side effect of emergent DSA (90%), perhaps because the angiography procedure was performed in the highly agitated cerebral arteries during the acute stages of SAH or the vasospasm was just the pathological course of SAH itself instead of angiography.^[15] In our opinion, due to the very low complication rate, we suggest that DSA can be performed safely for pathological diagnosis in the acute stage of SAH.

It is undisputed that intracranial aneurysm is the primary cause of SAH.^[5,11] Our cohort is consistent with this feature. Older patients with hypertension appeared to be more susceptible to aneurysmal SAH. This finding may indicate that higher age is an important risk factor for cerebrovascular disease and that hypertension is involved in aneurysm formation and rupture. Most studies have demonstrated that female gender is a recognized risk factor for the occurrence of aneurysmal SAH.^[16-20] Although the female-to-male ratio was approximately equal in our cohort, there was a gender difference between aneurysmal and nonaneurysmal SAH patients. The proportion of females was less in nonaneurysmal SAH patients. This demographic difference suggests that the underlying physiologic or anatomic processes of gender influence may be uniquely predisposed to either aneurysmal SAH or nonaneurysmal SAH.

For aneurysm location, anterior and posterior communicating arteries were the most common sites in aneurysmal SAH patients in this cohort. Middle cerebral artery bifurcation was another predominant site. These results are consistent with previous studies.^[21-24] These three anatomical locations are susceptible to intracranial aneurysm due to the morphologic vulnerability and blood flow feature in the Willis circle, or because of arterial bifurcation. The finding that the proportion of posterior circulation aneurysms was lower

has also been reported in previous studies, but still needs to be interpreted with caution due to the high mortality rate of those patients with ruptured posterior circulation aneurysms while on their way to hospital.^[9,10,12]

Previous studies reported that the majority of patients with nonaneurysmal SAH were in good clinical condition on admission.^[25-27] We replicated the same result with a lower Hunt–Hess score and modified Fisher’s grade in nonaneurysmal SAH patients and most of the nonaneurysmal SAH were PNSAH or had uncertain sources (76.5%). These data confirmed a favorable outcome in nonaneurysmal SAH patients compared with aneurysmal SAH patients.^[28,29]

The etiology of nonaneurysmal SAH varies, but usually there were no specific causes of bleeding in most of the nonaneurysmal SAH cases.^[30] In our series, unknown sources of SAH account for approximately 76.5% of patients with nonaneurysmal SAH due to the negative initial angiogram, and PNSAH, which is a unique subset of SAH pattern, accounts for 13% of total nonaneurysmal SAH cases. According to the previous reports, the positive rate of repeated angiography for PNSAH was only 0–7%; however, 8–46% of non-PNSAH cases with negative initial angiogram might have positive findings during the second angiography.^[30] Our results were consistent with those reports. None of the PNSAH were found to harbor intracranial aneurysms through repeated angiograms in our series. These findings strongly indicated that PNSAH was less likely to be associated with intracranial aneurysms.^[30] The 13.5% positivity rate of repeated angiograms in non-PNSAH cases in our series also supports the necessity of further radiological examination for such kind of patients.

In the current study, only 23.5% of nonaneurysmal SAH cases had positive initial angiographic findings, and AVM and Moyamoya disease are the major sources of bleeding among them. As described in previous studies, rupture of superficial AVM could result in SAH, especially if there is an associated aneurysm in the nidus, but Moyamoya disease was rarely mentioned in reports beyond Asia. However, in previous decades, the number of confirmed Moyamoya disease has dramatically increased in Asia with a considerable group of patients presenting with SAH.^[31,32] In our series, Moyamoya disease was the second most prevalent specific cause of nonaneurysmal SAH at a level similar to AVM, indicating the unique etiologic distribution features of SAH in China.

There are several limitations in our study. First, this is a descriptive cross-sectional study, lacking information on further treatment and outcomes. Second, the participating hospitals in this study were all large comprehensive hospitals. However, usually patients were firstly sent to either a district hospital or community hospital instead of large comprehensive hospitals. Therefore, the representativeness of the cohort in our study might be compromised.

In conclusion, we investigated the epidemiological features of nontraumatic spontaneous SAH in China and demonstrated that DSA can be performed safely for pathological diagnosis

in the acute stage (≤ 3 days) of SAH. Ruptured intracranial aneurysm was the major cause of SAH in China. Most of the ruptured aneurysms detected by DSA are located in the AComA, PComA, and MCA. Nonaneurysmal SAH cases have better neurological status compared with aneurysmal cases. The majority of nonaneurysmal SAH have no specific causes, including PNSAH. AVM and Moyamoya disease may be secondary positive pathological causes of SAH in China except for intracranial aneurysms.

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Conflicts of interest

There are no conflicts of interest.

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