Clinical Study

Does non-perimesencephalic type non-aneurysmal subarachnoid hemorrhage have a benign prognosis?

Dong-Hun Kang, Jaechan Park, Sun-Ho Lee, Seong-Hyun Park, Yong-Sun Kim, In-Suk Ham

Department of Neurosurgery, School of Medicine, Kyungpook National University, 50, Samduk-2-ga, Jung-gu, Daegu, 700-721, Korea

Keywords: Angiography-negative Perimesencephalic Prognosis Subarachnoid hemorrhage

Article history:
Received 15 August 2008
Accepted 5 October 2008

Abstract

We reviewed and compared the clinical course and long-term prognosis of patients with non-aneurysmal subarachnoid hemorrhage (SAH) with and without a perimesencephalic pattern of hemorrhage on CT scan. In 876 patients with spontaneous SAH, 52 (5.9%) were diagnosed with non-aneurysmal SAH. Based on their CT scans, the SAH was classified as perimesencephalic non-aneurysmal SAH (PNSH) in 23 patients and non-perimesencephalic (non-PNSH) in 29 patients. The patients in the non-PNSH group were further divided into diffuse type (19 patients) and localized type (10 patients). We performed follow-up three-dimensional-CT angiography (3D-CTA) in all possible patients at least 1 year after the attack. The PNSH group had a lower rate of acute hydrocephalus (8.7%) and angiographic vasospasm (0%) complications than the non-PNSH group (37.9% and 27.6%, respectively). Only one case of rebleeding occurred in the non-PNSH group. No demonstrable source of bleeding was found on follow-up 3D-CTA, which was performed 1 year after the attack. All patients with non-aneurysmal SAH had similarly favorable long-term functional outcomes. Based on our study, patients with non-PNSH have a more complicated clinical course than those with PNSH. However, the long-term prognosis was similarly favorable for both the PNSH and non-PNSH in limited circumstances when they showed normal findings on a series of two-dimensional and 3D angiographic work-ups.

1. Introduction

Spontaneous subarachnoid hemorrhage (SAH) is mostly caused by rupture of a saccular aneurysm, but conventional angiography fails to reveal an aneurysm in about 15% of patients with spontaneous SAH. In general, specific therapy cannot be offered to these patients and they are therefore treated with conservative therapy alone. The clinical course of spontaneous SAH varies according to location and amount of hemorrhage observed on CT scans. Van Gijn et al. reported a benign subgroup of patients with SAH of unknown origin, called perimesencephalic SAH. Perimesencephalic SAH is characterized by a CT scan pattern of hemorrhage restricted to the perimesencephalic or prepontine cisterns and accounts for 20% to 68% of all patients with angiography-negative SAH. However, other types of angiography-negative SAH might be susceptible to complications, such as rebleeding, vasospasm, and hydrocephalus. One aim of this study is to compare the clinical course of angiography-negative SAH patients with and without a perimesencephalic pattern of hemorrhage on CT scans.

Repeat angiography is usually performed about 2 weeks after ictus in most centers, and it usually yields negative results. In several published series, patients with angiography-negative SAH have a more favorable prognosis than those with a demonstrable bleeding source. However, these patients could potentially suffer fatal rebleeding and long-term disability, hence their long-term prognosis remains uncertain. Moreover, most previous studies investigating the prognosis of angiography-negative SAH were restricted to evaluating functional grades (modified Rankin scale [mRS] or Activity of Daily Living [ADL] scale).

We aimed to provide evidence of a benign prognosis in these patients. Therefore, all patients diagnosed with angiography-negative SAH were assessed using three-dimensional CT angiography (3D-CTA) during follow-up. The other aim of this study was to evaluate, functionally and radiologically, the prognosis of the patients with angiography-negative SAH.

2. Materials and methods

From January 2001 to June 2005, 876 patients who presented with spontaneous SAH were admitted to the Neurosurgical Department of Kyungpook National University. Each patient was
diagnosed with SAH using CT scan. In 824 of these patients, diagnostic studies demonstrated saccular aneurysms or other sources responsible for the bleeding. Initial conventional angiography revealed the cause of bleeding in 815 patients. The remaining 61 patients with negative findings on the initial angiogram were evaluated using a serial diagnostic algorithm (Fig. 1), and the cause of hemorrhage was discovered in 9 patients (14.8%). Detailed findings of these 9 patients are not described here. After these detailed work-ups, the remaining 52 patients who showed normal findings on 2 consecutive conventional angiograms and 2 follow-up 3D-CTAs were described as “non-aneurysmal SAH” and included in our study. We excluded the patients with SAH secondary to head trauma, ruptured arteriovenous malformation, ischemic stroke, tumors, and blood dyscrasias. We also excluded patients with technically defective angiographic results (without four-vessel or three-vessel angiographic findings) and whose clinical data were not available.

We collected information concerning the patients' demographics (age and sex) and clinical data (previous medical history, precipitants of SAH, severity and location of headache, neurological symptoms and signs). The severity of SAH was assessed using the Hunt and Hess grading system\textsuperscript{21} and the CT scan-based grading system proposed by Fisher et al.\textsuperscript{22} Furthermore, we classified the patients with non-aneurysmal SAH into three groups according to distribution of the hemorrhage on initial CT scan (Fig. 2) as follows:

(i) Perimesencephalic non-aneurysmal SAH (PNSH)\textsuperscript{12,23}: the center of the hemorrhage was located ventral to the brain stem mainly in the interpeduncular cistern, with or without

---

**Fig. 1.** Schematic diagram of the diagnostic algorithm for patients with spontaneous subarachnoid hemorrhage (SAH). Patients with negative findings on four consecutive angiographic examinations and MRI including diffusion-weighted image (DWI) and contrast-enhanced T1-weighted images (T1-WI) are diagnosed as “non-aneurysmal SAH”. 3D-CTA = three-dimensional CT angiography.

**Fig. 2.** Typical CT scans for each group of non-aneurysmal subarachnoid hemorrhage: (A) perimesencephalic, (B) diffuse type, (C) localized type – interhemispheric, and (D) localized type – sylvian.
extension to the ambient, chiasmatic and horizontal part of the sylvian cisterns and without intraventricular blood, except for the blood resulting from sedimentation effects.

(ii) Diffuse-type non-aneurysmal SAH (DNSH): the hemorrhage was centered on the basal cisterns and spread to the sylvian cisterns, interhemispheric cisterns, and cerebellopontine angle cisterns.

(iii) Localized-type non-aneurysmal SAH (LNSH): the hemorrhage was localized on either the sylvian cistern or interhemispheric cistern.

Changes in ventricular size on serial CT scans, incidence of rebleeding, angiographic vasospasm, and delayed ischemic deficit were investigated and compared between the groups. All patients were treated conservatively. Absolute bed rest, analgesics, laxatives, and minor tranquilizers were prescribed for at least 2 weeks.

During the outpatient visits, we interviewed the patients individually and asked questions regarding possible SAH episodes. Neurological findings were also assessed at that time. Follow-up 3D-CTA was performed in all possible patients, and long-term functional outcome was evaluated using the mRS. The results of these evaluations were then compared between groups.

3. Results

The 52 patients with non-aneurysmal SAH included 28 men and 24 women who ranged in age from 27 years to 74 years (mean age, 55.4 years). CT scans showed PNSH in 23 patients (44.2%) and non-PNSH in 29 patients (55.8%). Nineteen patients with non-PNSH had grade 3 or 4 SAH was observed in 21.7% of the patients with PNSH and 82.8% of those with non-PNSH (Table 1).

3.1. Clinical course of the non-aneurysmal SAH patients

We investigated the relationship between CT scan class and acute complications of non-aneurysmal SAH. Acute hydrocephalus developed more frequently in the patients in the non-PNSH group (p = 0.026, odds ratio [OR] = 6.42). Two (8.7%) of the patients in the PNSH group developed angiographic vasospasm; however, 8 patients (27.6%) in the non-PNSH group showed spasm (Table 2). All patients who showed angiographic vasospasm were clinically stable and none experienced delayed neurological worsening. Transcranial Doppler examination was carefully repeated and showed normalization within a few days.

Only one patient had an episode of rebleeding, which occurred 2 months after the initial hemorrhage. This 50-year-old male presented with Hunt and Hess grade 2, Fisher grade 3, and DNSH. The source of bleeding was not revealed on a full series of angiographic examinations, and no complications occurred during admission. Following conservative therapy for 2 weeks, the patient recovered well and was discharged home. Two months later, he revisited our emergency center with complaints of sudden-onset thunderclap headache and diagnosed with Fisher grade 2, DNSH. Additional conventional angiography and 3D-CTA were performed but were normal, and he was discharged in good condition. Follow-up 3D-CTA was performed 1 year from onset, and was also normal. His functional activity is now the same as before the SAH (mRS = 1).

3.2. Long-term outcome for non-aneurysmal SAH patients

The mean duration of follow-up was 62 months (range 36–89 months). In this series, the long-term outcomes of non-aneurysmal SAH patients were evaluated by two methods. 3D-CTAs were performed at least 1 year after the attack, and functional outcomes were assessed according to the modified Rankin scale (mRS) at least 3 years after the onset of SAH. Two PNSH patients did not present for follow-up visits. However, the present functional status of these patients could be assessed by telephone interview. Three patients had died during the follow-up period, 1 due to a fatal malignancy (gastric cancer) and 2 as a result of septic complications in a nursing home.

As shown in Table 2, 47 (90.4%) of the patients with non-aneurysmal SAH experienced a good outcome (mRS 0–2), and no significant relationship was shown between functional outcome and CT class (p = 0.251). Follow-up 3D-CTA was performed in 47 of the 52 patients 1 year after the onset of SAH, as two patients were lost during the follow-up period and three patients died. Follow-up 3D-CTA did not reveal an occult source of bleeding in any patient.

3.3. Comparison of complications and long-term outcome between diffuse and localized type non-PNSH patients

We found two subsets of patients with non-PNSH: diffuse and localized. The patients with DNSH developed acute hydrocephalus more frequently than those with LNSH (p = 0.025, OR = 10) (Table 3).
angiography. Neurological worsening associated with this scenario of large intradural arteries 3 to 14 days after SAH, as seen on bleeding rate after non-aneurysmal SAH. However, 27.6% (8/29) of non-PNSH subjects had amount of SAH might influence the development of vaso-

grade (3 or 4). Clinical vasospasm following angiogram-negative non-PNSH group, and had larger amounts of SAH or higher Fisher angiographic vasospasm was observed in 8 of the patients with non-aneurysmal SAH.35 In the present series, clinical vasospasm was not observed, but angiographic vasospasm has been reported less frequently as a complication of PNSH in 1% to 5% of patients.8 However, angiographic vasospasm has been reported more frequently than clinical vasospasm in patients with non-aneurysmal SAH; from 3% to 30%.28–32 Both CT scan class and the amount of SAH might influence the development of vasospasm.33,34 However, 27.6% (8/29) of non-PNSH subjects had angiographic vasospasm in our series, and the rate is similar to that of aneurysmal SAH.35

The incidence of hydrocephalus has been reported to be 0% to 15% in patients with non-aneurysmal SAH.5,36 In our series, 13 (25%) of the total developed acute hydrocephalus and 3 of them required a shunt operation. This rate is somewhat higher than that of previous studies and similar to the incidence of acute hydrocephalus in patients with aneurysm rupture.35 This result suggests that whether the SAH originates from an aneurysm rupture or not has little influence on the development of acute hydrocephalus. In addition, we found significant associations between CT scan class and the development of acute hydrocephalus; 8.7% (2/23) in PNSH and 37.9% (11/29) in non-PNSH (p = 0.026).

In summary, our results confirmed that patients with non-aneurysmal SAH have a better clinical course, especially in terms of rebleeding and clinical vasospasm, than those with aneurysm rupture. However, the incidence of acute hydrocephalus in patients with non-aneurysmal SAH is similar to that after aneurysm rupture. Additionally, non-aneurysmal SAH constitutes a heterogeneous group of patients, both PNSH and non-PNSH. Subjects with PNSH had a significantly better in-hospital course (lower incidence of hydrocephalus, angiographic vasospasm) than those with non-PNSH.

4. Long-term outcome of non-aneurysmal SAH patients

The reported long-term prognosis of patients with non-aneurysmal SAH is better than for those with aneurysm rupture.1,12,20,36,37 In the present series, we confirmed the overall good prognosis of patients with non-aneurysmal SAH. A good functional outcome (mRS 0–2) was observed in 22 of the 23 patients with PNSH. Even in subjects with non-PNSH and with a relatively worse in-hospital course, 25 of 29 showed good functional outcomes at least 3 years after the onset of SAH. Additionally, we performed 3D-CTA to ascertain the benign prognosis of non-aneurysmal SAH at least one year after the onset. No demonstrable source of bleeding was visualized on the follow-up 3D-CTA.

According to recent reports, the sensitivity and specificity of 3D-CTA for detecting cerebral aneurysm is almost equal to that of conventional angiography. It has even greater sensitivity for finding very small-sized aneurysms due to the technical limitations of conventional angiography. To discover aneurysms of 5 mm or less, conventional angiography requires ideal projection in order to visualize the aneurysm sac, however, this cannot be obtained or is not routinely checked as a part of an aneurysm work-up.38,39 Our result serves as additional evidence for the benign prognosis of patients with non-aneurysmal SAH and also supports previous reports that the causative source of non-aneurysmal SAH might originate from angiographically unidentifiable lesions, such as thrombosis of an aneurysmal orifice or sac, permanent destruction or self-repair of a microaneurysm or microangioma at the time of hemorrhage, venous bleeding, or other causes.40,41

4.3. Comparison of complications and long-term outcome between diffuse and localized non-PNSH patients

We found two subsets of patients in the non-PNSH group: 10 were in the LNSH group and 19 were in the DNSH group. The DNSH group showed a significantly higher incidence of acute hydrocephalus than the LNSH group. No significant difference was found in the rate of other complications or long-term outcome between the two groups. Especially when treating the LNSH group, we had a high suspicion that an occult source of bleeding might be found. Jafar et al. reported the result of explorative surgery in six patients with SAH who underwent multiple negative angiograms but their SAH patterns, which were similar to those of our LNSH patients, were highly suspicious for the presence of an aneurysm and they discovered aneurysmal sources in five cases.15 Every four patients with interhemispheric blood had an anterior communicating artery aneurysm, and a middle cerebral artery aneurysm was found in one patient with clots in the sylvian fissure. Besides this report, several authors stressed the need for explorative craniotomy in non-PNSH patients in cases of repeated bleeding or localized hemorrhages, as in our LNSH group.38,42 Despite our strong suspicions and sophisticated work-ups on the patients with LNSH,

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison between localized and diffuse type in non-PNSH patients: Fisher grade on initial CT scan, complications and long-term outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LNSH (n = 10)</td>
</tr>
<tr>
<td>Fisher grade</td>
<td>Number (%)</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>3</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>4</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
</tr>
<tr>
<td>Rebleeding</td>
<td>–</td>
</tr>
<tr>
<td>Acute hydrocephalus</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Angiographic vasospasm</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Modified Rankin Scale scores</td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>3–6</td>
<td>1 (10.0)</td>
</tr>
</tbody>
</table>

DNSH = diffuse-type non-aneurysmal subarachnoid hemorrhage, LNSH = localized-type non-aneurysmal subarachnoid hemorrhage, NS = not significant, PNSH = perimesencephalic non-aneurysmal subarachnoid hemorrhage.

Statistical significance test was done by the Fisher exact test.

However, the rate of rebleeding and angiographic vasospasm was not significantly associated with their CT scan class. Most of the patients (86.2%) in the two groups showed favorable long-term outcomes, and no significant relationship was found between their prognosis and CT scan class.

4. Discussion

4.1. Clinical course of non-aneurysmal SAH patients

In our series, only 1 patient (1.9%) in the DNSH group experienced a second episode of SAH 2 months after the first attack, and further angiography could not reveal the source of bleeding. The incidence of rebleeding after non-aneurysmal SAH has been reported in 2.8% to 6.8% of cases and is significantly lower than that of aneurysmal SAH.10,15,24–26 Due to the extremely low rate of rebleeding in our study, we could not identify a relationship between rebleeding and CT scan class, but our finding confirms the low rebleeding rate after non-aneurysmal SAH.

Cerebral vasospasm required further definition. The term “angiographic vasospasm” is used to describe reduction of the caliber of large intradural arteries 3 to 14 days after SAH, as seen on angiography. Neurological worsening associated with this scenario is more correctly called “clinical” or “symptomatic” vasospasm.27 In the present series, clinical vasospasm was not observed, but angiographic vasospasm was observed in 8 of the patients with non-aneurysmal SAH (15.4%). Notably, all 8 of them were in the non-PNSH group, and had larger amounts of SAH or higher Fisher grade (3 or 4). Clinical vasospasm following angiogram-negative SAH has been reported in 5% to 21% of patients,24,25 and it has been reported less frequently as a complication of PNSH in 1% to 5% of patients.5 However, angiographic vasospasm has been reported more frequently than clinical vasospasm in patients with non-aneurysmal SAH; from 3% to 30%.28–32 Both CT scan class and the amount of SAH might influence the development of vasospasm.33,34 However, 27.6% (8/29) of non-PNSH subjects had angiographic vasospasm in our series, and the rate is similar to that of aneurysmal SAH.35

In summary, our results confirmed that patients with non-aneurysmal SAH have a better clinical course, especially in terms of rebleeding and clinical vasospasm, than those with aneurysm rupture. Additionally, non-aneurysmal SAH constitutes a heterogeneous group of patients, both PNSH and non-PNSH. Subjects with PNSH had a significantly better in-hospital course (lower incidence of hydrocephalus, angiographic vasospasm) than those with non-PNSH.
no additional occult aneurysm was found in our series. Our findings might conflict with the above-mentioned reports. In our opinion, such discrepancy could originate from the sensitivity of angiographic studies. In the 1980s or 1990s, when the aforementioned articles were reported, the use of three-dimensional (3D) angiography was not widespread, so they may have missed the hidden source of the aneurysm due to the technical limitations of two-dimensional (2D) conventional angiography. However, our criteria for diagnosing “non-aneurysmal SAH”, normal findings on two conventional angiograms and two 3D-CTAs, were highly restrictive, hence the possibility of a false negative finding was minimal. Therefore, we might suggest that the non-PNSH patients also have a benign prognosis if they show negative findings on a detailed series of 2D and 3D angiographic exams, even if the hemorrhages are localized in the sylvian or interhemispheric cisterns.

4.4. Limitations of this study and future direction

Despite our restrictive criteria for diagnosing “non-aneurysmal SAH” and performance of long-term follow-up 3D-CTAs for proving benign prognosis, this study has some limitations. This study is retrospective, therefore, selection bias and protocol deviations were inevitably present. Due to the relatively small numbers of patients, this study lacks sufficient power to accurately predicate the benign prognosis of non-aneurysmal SAH. Finally, we did not perform 3D rotational angiography. The role of 3D rotational angiography appears promising recently, so further data on its use in patients with non-aneurysmal SAH are needed.

5. Conclusion

Based on our data, patients with PNSH have an uncomplicated clinical course and those with non-PNSH have a higher rate of acute complications, especially in terms of angiographic vasospasm and acute hydrocephalus. One case of rebleeding was found in the non-PNSH group. However, the long-term prognoses were similarly favorable for both the PNSH and non-PNSH groups at least 3 years after the onset of SAH, as confirmed by 3D-CTA. This similarity is favorable for both the PNSH and non-PNSH groups at least 3 years after the onset of SAH, as confirmed by 3D-CTA. This finding may be due to the advancement of angiographic techniques, including 3D-CTA, and to the decreasing incidence of false-negative results. Undoubtedly, all clinicians should be highly suspicious of patients with non-aneurysmal SAH, especially those with non-PNSH. Nevertheless, our results might indicate a benign prognosis for both PNSH and non-PNSH patients in limited circumstances when they show normal findings on a series of 2D and 3D angiographic work-ups.

References