Increasing numbers of nonaneurysmal subarachnoid hemorrhage in the last 15 years: antithrombotic medication as reason and prognostic factor?

Juergen Konczalla, MD, Sepide Kashefiolasl, MD, Nina Brawanski, MD, Christian Senft, MD, PhD, Volker Seifert, MD, PhD, and Johannes Platz, MD

Department of Neurosurgery, Goethe University Hospital, Frankfurt, Germany

OBJECTIVE Subarachnoid hemorrhage (SAH) is usually caused by a ruptured intracranial aneurysm, but in some patients no source of hemorrhage can be detected. More recent data showed increasing numbers of cases of spontaneous nonaneurysmal SAH (NASAH). The aim of this study was to analyze factors, especially the use of antithrombotic medications such as systemic anticoagulation or antiplatelet agents (aCPs), influencing the increasing numbers of cases of NASAH and the clinical outcome.

METHODS Between 1999 and 2013, 214 patients who were admitted to the authors’ institution suffered from NASAH, 14% of all patients with SAH. Outcome was assessed according to the modified Rankin Scale (mRS) at 6 months. Risk factors were identified based on the outcome.

RESULTS The number of patients with NASAH increased significantly in the last 15 years of the study period. There was a statistically significant increase in the rate of nonperimesencephalic (NPM)–SAH occurrence and aCP use, while the proportion of elderly patients remained stable. Favorable outcome (mRS 0–2) was achieved in 85% of cases, but patients treated with aCPs had a significantly higher risk for an unfavorable outcome. Further analysis showed that elderly patients, and especially the subgroup with a Fisher Grade 3 bleeding pattern, had a high risk for an unfavorable outcome, whereas the subgroup of NPM-SAH without a Fisher Grade 3 bleeding pattern had a favorable outcome, similar to perimesencephalic (PM)–SAH.

CONCLUSIONS Over the years, a significant increase in the number of patients with NASAH has been observed. Also, the rate of aCP use has increased significantly. Risk factors for an unfavorable outcome were age > 65 years, Fisher Grade 3 bleeding pattern, and aCP use. Both “PM-SAH” and “NPM-SAH without a Fisher Grade 3 bleeding pattern” had excellent outcomes. Patients with NASAH and a Fisher Grade 3 bleeding pattern had a significantly higher risk for an unfavorable outcome and death. Therefore, for further investigations, NPM-SAH should be stratified into patients with or without a Fisher Grade 3 bleeding pattern. Also, cases of spontaneous SAH should be stratified into NASAH and aneurysmal SAH.

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KEY WORDS nonaneurysmal subarachnoid hemorrhage; nonperimesencephalic; anticoagulation; antiplatelet agent; Fisher Grade 3; vascular disorders

SUBARACHNOID hemorrhage (SAH) is usually caused by intracranial aneurysm rupture. However, in up to 20% of patients with SAH, results of cerebral angiography, CT, and MRI are negative for aneurysms or other vascular malformations. More recent data show an increasing number of cases of spontaneous SAH as well as nonaneurysmal SAH (NASAH). Long-term dipyridamole and warfarin use were associated with an increased risk for aneurysmal SAH (aSAH), whereas the data for low-dose acetylsalicylic acid (LDA) were inconsistent. Therefore, we analyzed our institutional database for patients suffering from angiography-negative SAH. The aim of the study was to identify risk factors for the increase of NASAH as well as analyze outcome.

ABBREVIATIONS aCP = systemic anticoagulation or antiplatelet agent; aSAH = aneurysmal subarachnoid hemorrhage; CVS = cerebral vasospasm; DCI = delayed cerebral infarction; DSA = digital subtraction angiography; LDA = low-dose acetylsalicylic acid; mRS = modified Rankin Scale; NASAH = nonaneurysmal SAH; NPM = nonperimesencephalic; PM = perimesencephalic; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.


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Methods

All patients (n = 1493) with spontaneous SAH between 1999 and 2013 admitted to our institution were screened. Patients with trauma-related SAH and patients in whom the bleeding sources were determined to be an aneurysm or vascular malformation were excluded from the study.15,16 SAH was diagnosed by CT or lumbar puncture. Patient characteristics, treatments, radiological features, and outcomes were prospectively entered into our neurovascular database. The study was approved by the local ethics committee.

All patients underwent angiography and, after it became available in 2002, 3D digital subtraction angiography (DSA) of at least 4 vessels was also used to rule out intracranial bleeding sources.12 Generally, the angiography was repeated once: in patients with Fisher Grade 3 bleeding pattern, regularly 14 days after the ictus, and in some patients again at 2 months after the ictus. Additionally, spinal MRI was performed to rule out a spinal bleeding source.

On admission, patients were divided into good admission status (World Federation of Neurosurgical Societies [WFNS] Grades I–III) and poor admission status (WFNS Grades IV–V). Outcome was assessed according to the modified Rankin Scale (mRS) after 6 months and stratified into favorable (mRS Score 0–2) and unfavorable (mRS Score 3–6).

We defined a perimesencephalic (PM) hemorrhage according to van Gijn et al.23 and Rinkel et al.19 if the hemorrhage was located in front of the brainstem, mainly in the interpeduncular cistern. In nonperimesencephalic (NPM) hemorrhages, blood was not located mainly in the interpeduncular cistern but in the basal cisterns, Sylvian cistern, interhemispheric cistern, or convexity, or the patient had CT-negative and lumbar puncture–positive bleeding. We also stratified NPM-SAH cases into patients with a Fisher Grade 3 bleeding pattern or a non–Fisher Grade 3 bleeding pattern.

Statistical Analysis

Data analysis was performed using the computer software package SPSS version 22 (IBM Corp.). Unpaired t-tests were used for parametric statistics. Categorical variables were analyzed in contingency tables using Fisher’s exact test. For trend statistics, the Mantel-Haenszel test was used. Results with p ≤ 0.05 were considered statistically significant. Due to the low number of cases, we divided the study period into 3-year intervals to be able to compare the data.

Results

Patient Characteristics

Between 1999 and 2013, 214 patients who were admitted to our institution were found to have NASAH based on initial diagnostic workup (see flow diagram show in Fig. 1). Patients’ characteristics, including bleeding type, age, sex, use of antithrombotic medications such as systemic anticoagulation or antiplatelet agents (aCPs), hypertension, and clinical outcome are presented in detail in Table 1.

In the baseline interval from 1999 to 2001, 20 patients presented with a NASAH. In the following 3 years (2002–2004), 70% more patients (n = 34) were found to have NASAH. The number of NASAH cases increased significantly over the study intervals to 65 (225%) in the last interval (2011–2013) (Fig. 2; Table 2). Over the entire study period, the ratio of patients with NASAH compared with all patients with SAH increased from 9% to over 20%. Trend statistics showed a highly significant linear trend for this increase in NASAH (p < 0.001; Fig. 3). The proportion of patients older than 65 years (approximately 25%); Table 2) was stable, and statistics showed no significant trend toward a higher admission rate.

We identified elderly patients, aCP use, and Fisher Grade 3 bleeding pattern as significant prognostic factors for an unfavorable outcome (p < 0.01; Table 3).

SAH Pattern on Initial CT Scan

Overall, 46% of the patients had a PM-SAH and 54% of patients suffered from NPM-SAH (Table 1). Of all NASAH cases, the proportion of patients with NPM-SAH increased significantly over the study intervals, from 50% in 1999–2001 to 71% in 2011–2013 (p < 0.05), whereas the rate of PM-SAH decreased significantly from 50% to 29%. For patients with NPM-SAH, only a trend toward an unfavorable outcome was detected, but for the subgroup of patients with a Fisher Grade 3 bleeding pattern, a significantly higher mortality rate (p < 0.01) and a significantly higher risk for an unfavorable outcome were detected (p < 0.01; Table 3). Also, the observation of Fisher Grade 3 bleeding patterns increased over the study intervals, from a rate of 15% to 26%, but did not achieve statistical significance.

Arterial Hypertension

In the first study interval, 30% of the patients had hypertension. In the subsequent years, the rate of hypertension slightly increased to 51% of patients, which was not a significant trend (p > 0.1; Fig. 2; Table 2). Hypertension neither influenced the outcome nor the type of bleeding (PM- or NPM-SAH; Tables 1 and 3).

Use of Systemic Anticoagulation or Antiplatelet Agents

The use of aCPs increased steadily and significantly, from 5% of cases in 1999–2001 to 32% of cases in 2011–2013 (Fig. 2; Table 2). Significantly more patients with NPM-SAH were treated with aCPs (p < 0.01; Table 1), and these patients seem to have higher rates of cerebral vasospasm (CVS) and delayed cerebral infarctions (DCIs) (Table 4). Additionally, patients who received aCPs had a significantly higher mortality rate (21% vs 5% without aCP; p < 0.01; Table 4) and a significantly lower chance for favorable outcome (mRS 0–2, 63% vs 91% without aCP; p < 0.0001; Table 3).

Discussion

Subarachnoid hemorrhage without identification of a bleeding source is/was rare compared with aSAH and is assumed to have a good outcome.4,11,20,22 However, recent investigations have shown this condition increasing.15,16,18 Our institutional data from the last 15 years was analyzed,
and 214 patients suffering from angiography-negative SAH were identified. Most of the patients achieved a favorable outcome, but in the last years, we have observed a shift in the profile of patient characteristics. An increasing number of patients who were undergoing treatment with aCPs and exhibiting greater bleeding patterns (Fisher Grade 3) were admitted to our hospital.

Incidence of NASAH and SAH Pattern

Overall, in the present series, a favorable outcome was achieved in 85% of the patients with NASAH, which is comparable to other reported data. However, despite technical advancements in DSA, MRI, and CT technology over the study period, the number of patients with NASAH has increased significantly (Fig. 3). Also, the SAH bleeding pattern has changed significantly over the period intervals (Fig. 1). Whereas in the first interval 50% of the patients suffered from PM-SAH, in the last period (2011–2013) only 29% had PM-SAH. Meanwhile, the observation of Fisher Grade 3 bleeding patterns increased from 15% (1999–2001) to 26% (2011–2013). In patients suffering from NASAH, favorable outcomes were significantly associated with the SAH pattern on initial CT. A Fisher Grade 3 bleeding pattern represented a

| TABLE 1. Characteristics of 214 patients with nonaneurysmal SAH stratified by SAH location (perimesencephalic vs nonperimesencephalic)* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic                  | NASAH           | PM-SAH          | NPM-SAH         | p Value†        |
| No. of pts                      | 214             | 98 (46)         | 116 (54)        |                 |
| Mean age ± SD (yrs)             | 57 ± 14         | 55 ± 12         | 58 ± 15         | NS              |
| Female                          | 79 (37)         | 30 (31)         | 49 (42)         | NS              |
| HTN                             | 93 (43)         | 37 (38)         | 56 (48)         | NS              |
| aCP                             | 43 (20)         | 11 (11)         | 32 (28)         | <0.01           |
| Fav outcome                     | 182 (85)        | 88 (90)         | 94 (81)         | NS              |
| Death                           | 18 (8)          | 7 (7)           | 11 (9)          | NS              |

Fav outcome = favorable outcome; HTN = arterial hypertension; NS = not significant (p > 0.05); pts = patients.
* Values are n (%) unless otherwise indicated.
† Unpaired t-test for parametric statistics and Fisher’s exact test for categorical variables.
significantly higher risk for an unfavorable outcome (OR 3.2; Table 3) and death (OR 3.0) compared with a NPM non–Fisher Grade 3 bleeding pattern, as described earlier.13,16,25 A comparison between PM- and NPM-SAH revealed a trend towards an unfavorable outcome for NPM-SAH (p = 0.09), which supports recent data.1,16,25 The NPM-SAH group without a Fisher Grade 3 bleeding pattern had similar and often favorable outcomes (87%) compared with the PM-SAH group (90%; Table 1). Accordingly, patients with an NPM-SAH and without a Fisher Grade 3 bleeding pattern also had a significantly better outcome compared with patients with NPM-SAH and a Fisher Grade 3 bleeding pattern (p < 0.05, OR 2.7). Patients with a Fisher Grade 3 bleeding pattern had a significantly higher mortality rate compared with patients with NPM-SAH and without a Fisher Grade 3 bleeding pattern (p = 0.05, OR 3.7). Therefore, we recommend for further investigations a more detailed analysis of NPM-SAH, stratified to NPM-SAH with and without a Fisher Grade 3 bleeding pattern.

Whereas the use of newer CT scanners, offering greater detection capability, might be a reason for the increase of NPM-SAH, older CT scanners were also able to detect especially large bleeding patterns (Fisher Grade 3), which, nevertheless, are detected more often at present. Possible reasons for the increase of NPM-SAH may be hypertension and aCP use, but this could also be purely coincidental.

**Prognostic Factors**

As in other studies,15 in our investigations, elderly patients had a significantly higher risk for an unfavorable outcome (Table 3), but the proportion of elderly patients remained stable (approximately 25%; Table 2). Forty-three percent of the patients had arterial hypertension, aCP use, and patients > 65 years. In all groups the absolute number increased. Only a slight increase was detected for hypertension and patients > 65 years (similar to the increase of NASH), whereas the rate of patients treated with aCP increased significantly.

![Graph showing percent increase from interval 1999–2001 throughout the study period of patients with NASAH, with arterial hypertension, aCP use, and patients > 65 years. In all groups the absolute number increased. Only a slight increase was detected for hypertension and patients > 65 years (similar to the increase of NASAH), whereas the rate of patients treated with aCP increased significantly.](image)

**TABLE 2. Increase in NASAH, arterial hypertension, and aCP treatment throughout the study period**

<table>
<thead>
<tr>
<th>Study Intervals</th>
<th>No. of Pts w/ NASAH</th>
<th>% Pt Increase*</th>
<th>HTN, n (%)</th>
<th>% Pt Increase*</th>
<th>p Value†</th>
<th>Age &gt;65 Yrs, n (%)</th>
<th>% Pt Increase*</th>
<th>p Value†</th>
<th>Pts Treated w/ aCP, n (%)</th>
<th>% Pt Increase*</th>
<th>p Value†</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999–2001</td>
<td>20</td>
<td>6 (30)</td>
<td></td>
<td>5 (25)</td>
<td>1 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002–2004</td>
<td>34</td>
<td>70</td>
<td>12 (35)</td>
<td>100</td>
<td>20</td>
<td>NS</td>
<td>6 (18)</td>
<td>20</td>
<td>NS</td>
<td>4 (12)</td>
<td>300</td>
<td>NS</td>
</tr>
<tr>
<td>2005–2007</td>
<td>46</td>
<td>130</td>
<td>21 (46)</td>
<td>250</td>
<td>11 (24)</td>
<td>NS</td>
<td>12 (24)</td>
<td>140</td>
<td>NS</td>
<td>6 (13)</td>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>2008–2010</td>
<td>49</td>
<td>145</td>
<td>21 (43)</td>
<td>250</td>
<td>12 (24)</td>
<td>NS</td>
<td>12 (24)</td>
<td>140</td>
<td>NS</td>
<td>11 (22)</td>
<td>1000</td>
<td>NS</td>
</tr>
<tr>
<td>2011–2013</td>
<td>65</td>
<td>225</td>
<td>33 (51)</td>
<td>450</td>
<td>16 (25)</td>
<td>NS</td>
<td>200</td>
<td>200</td>
<td>NS</td>
<td>21 (32)</td>
<td>2000 &lt;0.05</td>
<td>9.1 (1.1–72)</td>
</tr>
</tbody>
</table>

* Calculated as increase relative to study interval 1999–2001.
Increasing antithrombotic medication and nonaneurysmal SAH tension, which is comparable to other reported data. Over the study intervals, the rate of patients with hypertension increased nonsignificantly (Fig. 2; Table 2). The outcome and mortality rate were similar for patients with or without hypertension as those observed in other reports. Hypertension in aSAH is associated with unfavorable outcome, whereas in NASAH, it seems not to be a prognostic factor (Table 3).

Another factor that may account for the increasing number of patients with NASAH and the enlarging amount of visible blood could be aCP use. The rate of patients being treated with aCPs has increased significantly (from 5% to 32%; Figs. 2 and 3; Table 2), but data for NASAH are scarce and mostly only describe higher blood volume and rebleeding rates, resulting in worse admission status and worse outcome. Data for aSAH also remain scarce and describe a worse outcome or nonreduced 30-day case fatality.

However, aCP use was significantly higher in the NPM-SAHA group compared with the PM-SAHA group (28% vs 11%; p < 0.01; Table 1). The slightly increased rate of CVS and DCI with aCP use could also be an indication for higher amounts of bleeding, without reaching statistical significance. Nonetheless, the population of patients treated with aCPs had a significantly higher mortality rate and a 5.7-times higher risk for an unfavorable outcome. Therefore, this indicates that aCP use is, at least, a prognostic factor.

**Reasons for Increased Numbers of NASAH**

The number of patients with NASAH increased sig-

**TABLE 3. Prognostic factors for outcome***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favorable Outcome</th>
<th>Unfavorable Outcome</th>
<th>p Value vs Favorable Outcome†</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>182 (85)</td>
<td>32 (15)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD (yrs)</td>
<td>55 ± 13</td>
<td>68 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>64 (35)</td>
<td>15 (47)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>75 (41)</td>
<td>18 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPM-SAHA w/o Fisher Grade 3</td>
<td>65 (36)</td>
<td>10 (31)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Fisher Grade 3</td>
<td>29 (16)</td>
<td>12 (38)</td>
<td>&lt;0.01</td>
<td>3.2 (1.4–7.2)</td>
</tr>
<tr>
<td>aCP use</td>
<td>27 (15)</td>
<td>16 (50)</td>
<td>&lt;0.0001</td>
<td>5.7 (2.6–12.8)</td>
</tr>
</tbody>
</table>

* Values are n (%) unless otherwise indicated.
† Unpaired t-test for parametric statistics and Fisher’s exact test for categorical variables.
significantly over the study intervals (225%) (Fig. 2; Table 2). Long-term dipyridamole and warfarin use were associated with an increased risk for aSAH, whereas the data for low-dose LDA in aSAH were inconsistent.\textsuperscript{10,14,21} Also, a recently published meta-analysis showed a higher risk for subdural hematoma in patients using vitamin K antagonists or LDA.\textsuperscript{5,6} In this study, the significant increase of NASAH was associated with a significant increase of use of aCPs (2000%; \( p < 0.05; \) Table 2), which was also associated with an increased rate of NPM (Table 1). Also, it is known that aCP use is associated with an increased SAH volume.\textsuperscript{17} Altogether, this suggests that aCP use may play an important role in the increase of NASAH.

Limitations
The study has several limitations. It is a retrospective, single-center, statistical analysis, but data were collected prospectively. Due to the retrospective design, the typical restrictions exist, such as the lack of data not documented initially in the medical records. Nonetheless, given that NASAH is a rare condition, the cohort is very large and also exhibited trend statistics showing a significant increase. Due to the low number of cases, we divided the study period into 3-year intervals to allow for comparison of the data, but statistics showed a significant trend in both modalities, per-period and per-year analysis. Therefore, the data seem to be reliable and valid.

However, the numbers of patients using aCPs are still low, and, therefore, it is not advisable to create subgroups to obtain more valid data for a causal relationship. No patients in this cohort received any of the newly available oral anticoagulants. The reasons for the observed increase of frequency and severity of NASAH could be coincidental to aCP use, and the exact pathogenic mechanism of NASAH is still unclear. Therefore, a combination of hypertension and aCP use may play a role, but a causal relationship cannot, thus far, be proven. Data from other centers are necessary to confirm our findings; however, for this rare condition, the cohort may be considered large. Thus, we advise that other institutes examine their patient cohort with these considerations in mind.

Conclusions
The number of patients in our cohort with NASAH has been increasing significantly over the last 15 years. Therefore, further studies investigating increasing number of cases of spontaneous SAH should stratify between NASAH and aSAH. Also, we identified significantly higher rates of aCP use, different types of bleeding (higher incidence of NPM-SAH), and higher volumes of bleeding (higher incidence of Fisher Grade 3 bleeding pattern). The use of aCPs was a negative prognostic factor and was associated with a significantly worse outcome and a higher mortality rate, whereas hypertension was not a prognostic factor. Also, elderly patients had a higher risk for an unfavorable outcome.

Patients with an NPM- SAH without Fisher Grade 3 bleeding pattern experienced an excellent outcome, similar to that of PM-SA H patients, whereas patients with a NPM- SAH with Fisher Grade 3 bleeding pattern had a high risk for an unfavorable outcome and death. Further investigations should stratify NPM-SA H to patients with or without Fisher Grade 3 bleeding pattern.

Acknowledgments
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References

TABLE 4. Rates of cerebral vasospasm, delayed cerebral ischemia, and mortality in patients with NASAH depending on use of aCP\textsuperscript{*}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Pts (n = 214)</th>
<th>w/o aCP (n = 171)</th>
<th>w/ aCP (n = 43)</th>
<th>p Value\textsuperscript{†}</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>42 (20)</td>
<td>32 (19)</td>
<td>10 (23)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>DCI</td>
<td>30 (14)</td>
<td>22 (13)</td>
<td>8 (19)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>18 (8)</td>
<td>9 (5)</td>
<td>9 (21)</td>
<td>&lt;0.05</td>
<td>4.8 (1.8–12.9)</td>
</tr>
</tbody>
</table>

\* Values are n (%) unless otherwise indicated.
\† Fisher’s exact test.
Increasing antithrombotic medication and nonaneurysmal SAH


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Konczalla. Acquisition of data: Konczalla, Kashefiolasl, Brawanski, Platz. Analysis and interpretation of data: Konczalla. Drafting the article: Konczalla. Critically revising the article: Senft, Seifert, Platz. Reviewed submitted version of manuscript: Senft, Seifert, Platz. Approved the final version of the manuscript on behalf of all authors: Konczalla. Statistical analysis: Konczalla. Administrative/technical/material support: Kashefiolasl, Brawanski, Platz. Study supervision: Seifert, Platz.

Correspondence
Juergen Konczalla, Department of Neurosurgery, Goethe University Hospital Frankfurt, Schleusenweg 2-16, Frankfurt am Main 60528, Germany. email: J.Konczalla@med.uni-frankfurt.de.