Sentinel Headache and the Risk of Rebleeding After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—The clinical significance of sentinel headaches in patients with subarachnoid hemorrhage (SAH) is still unknown. We investigated whether patients with a sentinel headache (SH) have a higher rate of rebleeding after SAH.

Methods—An SH was defined as a sudden, severe, unknown headache lasting ≥1 hour with or without accompanying symptoms, not leading to a diagnosis of SAH in the 4 weeks before the index SAH. Age, sex, smoking status, clinical grade, computed tomography (CT) findings, angiographic findings, placement of an external ventricular drain, and time to aneurysm obliteration were prospectively recorded. All rebleeding events were confirmed by CT. Outcome was assessed at 6 months according to the modified Rankin Scale.

Results—Of 237 consecutive patients with SAH, 41 (17.3%) had an SH. Rebleeding occurred in 23 (9.7%) of all patients. Patients with an SH had a 10-fold increased odds of rebleeding compared with patients without SH. Aneurysm size and the total number of aneurysms were also significantly associated with rebleeding. There were no differences in age, sex, smoking, CT or angiographic findings, external ventricular drain placement, or time to aneurysm obliteration between groups. Patients with rebleeding had a significantly worse outcome. Logistic regression revealed the presence of an SH as an independent risk factor for rebleeding.

Conclusions—In our study, patients with SAH who had an SH constituted a special group of patients with a 10-fold odds for early rebleeding. The presence of an SH may select candidates for ultraearly aneurysm obliteration or drug treatment. (Stroke. 2006;37:2733-2737.)

Key Words: intracranial aneurysm ■ minor leak ■ rebleeding ■ sentinel headache ■ subarachnoid hemorrhage

The presence of a severe, sudden headache, often referred to as a warning leak, minor leak, or sentinel headache (SH), during the days or weeks before subarachnoid hemorrhage (SAH) has been reported in 15% to 60% of all patients eventually admitted with an SAH.1,2 The clinical significance and pathophysiology of an SH have been a matter of debate. The proposed explanations for an SH range from changes in the wall of the aneurysm without rupture or rupture of an intracranial aneurysm causing minor SAH to “recall bias,” which is completely unrelated to SAH.3,4 The current mainstay of treatment of acute SAH consists of prevention of another bleed, because the rebleeding rate and associated mortality are exceedingly high.5-9 Despite the lack of prospective controlled data, most protocols favor early treatment in <48 to 72 hours after the ictus. Because the rebleeding rate may be highest immediately after SAH, some investigators have suggested a general policy of ultraearly surgery, which is unlikely to gain wide acceptance, because it does not provide treatment with the best team under the optimum circumstances for many patients.10 It would be of important clinical value to identify a subgroup of patients that is more likely than others to experience rebleeding.

The hypothesis of our study was that there is a causal relation between the aneurysm or SAH and the clinical sign of an SH; ie, patients with an SH may have more fragile aneurysms. Therefore, we investigated whether patients with an SH disproportionately often experience early rebleeding. This hypothesis was prospectively tested by investigating whether patients who presented with an SH before the index SAH indeed had a higher rate of rebleeding compared with those without an SH.

Subjects and Methods

Patient Population and General Patient Management

The study was approved by the ethics committee of the University of Frankfurt/Main, Germany. From May 1999 to May 2002, we included 237 consecutive patients with SAH proven by computed tomography (CT) or lumbar puncture. Information, including patient characteristics, treatment, radiological features, the presence of an SH, and rebleeding, was prospectively entered in an SPSS database.
(SPSS Institute, Inc, Chicago, Ill). Selection of patients for open or endovascular surgery was accomplished by an interdisciplinary team. We followed an early surgery strategy (24 to 48 hours) in patients of all clinical grades unless the patients were hemodynamically unstable or moribund. Early hydrocephalus was treated by external cerebrospinal fluid diversion. Routine surveillance included daily transcranial Doppler measurements and, in selected cases, multimodal monitoring of brain tissue O$_2$, regional cerebral blood flow (thermodilution microprobe), and interstitial metabolites (microdialysis). Attention was paid to administer sufficient fluid to maintain a high normal euvoletic status; however, a prophylactic hypertension-hypervolemia-hemodilution regimen was not instituted. All patients received nimodipine from the day of admission. Fludrocortisone was administered as an adjunct in case of hyponatremia, and desmopressin was used to control excessive diuresis. In cases of symptomatic vasospasm, hypervolemia was instituted and hypertension was induced with catecholamines. When hypertension-hypervolemia-hemodilution therapy failed, patients with focal vasospasm were selected for angioplasty. Outcome was assessed according to a modified Rankin Scale (mRS) after 6 months.

**Sentinel Headache**
A thorough history was taken of patients, their relatives or accompanying persons, general practitioners, and emergency or admitting doctors. We inquired about a sudden, severe headache of unknown character and intensity lasting at least 1 hour in the last 4 weeks before the index SAH that had never been experienced before. There had to have been improvement before the index SAH or another deterioration that led to a diagnosis of SAH. Such headaches and the lack of a proven diagnosis of SAH were defined as SHs. Contact with family members or relatives could be established within 24 hours and with primary care physicians within 3 days. If, after 3 days, no information could be obtained, the respective patient was regarded as not having experienced an SH.

**Rebleeding**
We included only CT-proven episodes of rebleeding. All CT scans were assessed by a senior neuroradiologist, and the amount of blood was compared with that on the preceding CT. The neuroradiologist was blinded to a history of SH. Cases with a high clinical suspicion of rebleeding but without confirmation by at least 2 subsequent CT scans were not included. Any deterioration (eg, new neurological deficit, a decrease in the level of consciousness, or severe headache) prompted emergency CT scanning. In the sedated and ventilated or comatose patients, any suspicious event, like bradycardia, and a sudden rise in blood pressure or the appearance of new blood on ventricular drainage led to CT scanning. All patients underwent CT scanning after clipping/intervention within <48 hours as well as at day 14 or at discharge. The CT scans performed at referring hospitals were included; ie, CT-proven rebleeding before hospitalization in our neurosurgical institution was also included. Rebleeding after aneurysm obliteration was not included.

**Data Analysis**
To test for an association with rebleeding, categorical variables were tested with Fisher exact test or $\chi^2$ test; continuous variables were subjected to the Mann-Whitney U test or a t test. A binary logistic-regression model for the prediction of rebleeding was used to find the most important baseline predictors. Results with $P<0.05$ were considered statistically significant. All calculations were made with a standard commercial software (SPSS Institute, Inc).

**Results**

**Patient Population**
Baseline characteristics, including age, sex, smoking habits, clinical status, and angiographic and CT imaging findings, are shown in Table 1. Noteworthy is the high rate (40.5%) of very ill patients who were admitted with a Hunt-Hess grade of 4 and 5.

**Rebleeding**
The overall rebleeding rate was 9.7%; ie, 23 of 237 patients experienced rebleeding before aneurysm obliteration (Table 2). Forty-one of all 237 patients (17.3%) had an SH before the index SAH (Table 2). Univariate analysis revealed that the presence of an SH, maximum aneurysm size, and the number of aneurysms an individual patient presented with were significantly associated with rebleeding (Table 3). There was a trend for an association with less rebleeding for aneurysms of the anterior circulation ($P=0.14$) and for increased rebleeding for patients in severer Hunt-Hess grades ($P=0.16$). There was no association between the frequency of rebleeding and patient age, sex, smoking habits, or findings on the initial CT scan as evaluated by Fisher grade (Table 3).

The in-hospital intervention of placement of an external ventricular drain or the time elapsed since the ictus to...
TABLE 3. Univariate Analysis of Variables as Predictors for Rebleeding

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Rebleeding (n=214)</th>
<th>Rebleeding (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH</td>
<td>26 (12.1)</td>
<td>15 (65.2)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Maximum aneurysm size, mm</td>
<td>6.9±4.7</td>
<td>11.2±9.2</td>
<td>0.002§</td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td>1.12±0.75</td>
<td>1.67±1.28</td>
<td>0.003†</td>
</tr>
<tr>
<td>Anterior circulation*</td>
<td>108 (64.3)</td>
<td>9 (45)</td>
<td>0.14†</td>
</tr>
<tr>
<td>Hunt-Hess grade</td>
<td>3.07±1.3</td>
<td>3.48±1.2</td>
<td>0.16‡</td>
</tr>
<tr>
<td>Smoking</td>
<td>110 (51.4)</td>
<td>9 (39.1)</td>
<td>0.42†</td>
</tr>
<tr>
<td>Female sex</td>
<td>127 (59.3)</td>
<td>12 (52.2)</td>
<td>0.51†</td>
</tr>
<tr>
<td>Fisher grade</td>
<td></td>
<td></td>
<td>0.60§</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>53.6±13.7</td>
<td>52.0±15.8</td>
<td>0.62‡</td>
</tr>
<tr>
<td>External ventricular drain placed</td>
<td>118 (55.1)</td>
<td>15 (65.2)</td>
<td>0.51†</td>
</tr>
<tr>
<td>Time to obliteration, h</td>
<td>Mean±SD</td>
<td></td>
<td>0.91‡</td>
</tr>
<tr>
<td></td>
<td>80±157</td>
<td>97±139</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>26.00</td>
<td>24.50</td>
<td></td>
</tr>
</tbody>
</table>

*Includes the anterior cerebral, middle cerebral, and internal carotid; †Fisher exact test; §Mann-Whitney U test; ¶χ² test.

TABLE 4. Time Between the Index SAH and Aneurysm Obliteration (Time at Risk) in Patients With and Without SH

<table>
<thead>
<tr>
<th>Variable</th>
<th>No SH (n=146)</th>
<th>SH (n=34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to aneurysm obliteration (time at risk, h)</td>
<td>79±160</td>
<td>95±133</td>
<td>0.51*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>26.00</td>
<td>38.00</td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Whitney U test.

Outcome

Overall outcome at 6 months was available for 212 patients. Rebleeding significantly increased the odds of death (OR, 2.6; 95% CI, 1.1 to 6.3; P=0.048), reduced the odds of survival with good outcome (mRS score <3; OR, 0.34; 95% CI, 0.13 to 0.92; P=0.041), and reduced the odds of survival with functional independence (mRS score <4; OR, 0.26; 95% CI 0.098 to 0.7; P=0.006; Table 6).

Discussion

In this prospective series of consecutive patients, the presence of an SH before the index SAH was associated with a significantly higher (~10-fold) incidence of rebleeding before aneurysm obliteration than in patients without an SH. We believe that this finding is important and may impact patient management.

Rebleeding

Ultraearly rebleeding that occurs before early aneurysm obliteration may still be underestimated and is responsible for poor outcome in many cases. Ultraearly aneurysm treatment is cumbersome, and to be able to select a patient population with an increased risk for rebleeding might be of marked clinical value.

Several studies have addressed the frequency of rebleeding and the issue of finding predictors of rebleeding. The current rebleeding rate of 9.7% is concordant with other recent series that followed a premise of early aneurysm obliteration, as well as with the 10.8% found in the control group of the multicenter tranexamic acid trial or the 12% found by Laidlaw and Siu.

It is somewhat lower than the 17.3% found by Fujii et al and somewhat higher than the 6.9% recently found by Naidech et al. It is much higher, however, than the 1.7% that was found in the large ISAT population. This might reflect the fact that ours is a tertiary care neurovascular center whose patient population is characterized by an overrepresentation of complex aneurysms, a 4 times higher frequency of aneurysms in the posterior circulation than in population-based studies, and an unequally higher proportion (40.5%) of very ill patients with a Hunt-Hess grade of 4 or 5.

It has not been shown, to our knowledge, that the total number of aneurysms a patient harbors on angiography at the time when one has ruptured is a risk factor for rebleeding. The explanation of this finding is not obvious; however, one might speculate that patients with several aneurysms have a more fragile vessel wall that is either prone to forming multiple aneurysms or prone to rebleeding after the aneurysm has already ruptured. There is also evidence that patients with multiple aneurysms may have a specific genetic pattern. After correction for other variables with logistic regression, the total number of aneurysms was significantly associated with rebleeding (P=0.02).

Conservative estimates on the risk of rebleeding of ruptured aneurysms are ~4% in the first day after SAH and then decreasing to 1% to 2% in the following weeks, accumulating at 30% to 50% for the first 3 months. However, the rate of rebleeding might be even higher in the first hours after SAH, probably highest within the first 6
hours, and already declining thereafter.\textsuperscript{5,10,12,18,19,20} In the current study, 40\% of rebleeding events occurred in the first 6 hours. Fujii et al.\textsuperscript{5} even found that 17.3\% of their patients experienced ultraearly rebleeding, with 87.1\% of these patients having rebleeding within 6 hours. This phenomenon would prompt either an ultraearly treatment regimen\textsuperscript{10} or other measures including medical treatment. Reconsidering the administration of tranexamic acid for a selected patient pool might be most promising in the near future.\textsuperscript{7} A vital parameter for the incidence of rebleeding is the time at risk, ie, the time from the index SAH to aneurysm obliteration. To exclude bias, we have shown that aneurysm obliteration did not occur later in patients with an SH (P=0.51). The distribution with the highest incidence on day 1 followed by an exponential decline and few cases of late aneurysm obliteration were equal in both groups (the Figure).

The time elapsed from the ictus to aneurysm obliteration was also not different (P=0.9) between patients with or without rebleeding, which makes a possible bias unlikely that a delay in treatment might be responsible for the higher incidence of rebleeding. In our opinion, this further highlights the notion that most rebleeding events occur very early and thus, escape the chance of prevention even with the current early obliteration treatment strategy.

Sentinel Headache
The frequency of 17.3\% of SH in the current study is consistent with the 19.9\% found by Jakobsson et al\textsuperscript{2} and is somewhat higher than the 11\% quoted in an analysis by Linn et al.\textsuperscript{4} We only counted patients as having experienced an SH if the information was received within the first 3 days after admission. This could have resulted in selection bias, and the actual number of patients with an SH might have been even higher in our population of very sick patients. However, we believe that this bias does not change the conclusion. This bias would even strengthen the findings if very sick patients experiencing a rebleeding event were erroneously regarded as not having experienced an SH, which is more likely to have been attributable to a restricted history taking in these very ill patients.

According to the current data, the presence of an SH might be the most important indicator for rebleeding. There are 3 other recent studies with a modern, early-treatment paradigm, which corroborate our findings. Linn et al.\textsuperscript{4} conducted a landmark study showing that rebleeding had distinct clinical and radiological features that were not present in patients admitted with a history of an SH and concluding that patients admitted with an SH are not simply admitted with a rebleed but that “recall bias” may be responsible for the notion of a warning headache. When we analyzed their data in retrospect as presented in the article regarding our hypothesis that patients with an SH have an increased risk of rebleeding, we found a significantly increased (2.8-fold) (P=0.011) relative risk (OR, 3.4) of rebleeding in patients with a history of SH compared with patients without. For interpretation, one has to keep in mind that the time at risk between the patients with and without a warning leak was not given in the article.

<table>
<thead>
<tr>
<th>MRS score</th>
<th>No Rebleeding (n=190)</th>
<th>Rebleeding (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (no symptoms)</td>
<td>19 (10)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>1 (minor symptoms)</td>
<td>57 (30)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>2 (some restriction)</td>
<td>23 (12.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3 (significant restriction)</td>
<td>13 (6.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4 (partly dependent)</td>
<td>15 (7.9)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>5 (fully dependent)</td>
<td>10 (5.3)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>6 (deceased)</td>
<td>53 (27.9)</td>
<td>11 (50)</td>
</tr>
</tbody>
</table>

Data are numbers and (percentages) of patients (P=0.01, $\chi^2$ test).
Another recent study found that there was significantly (P = 0.009) more often a positive history of a sentinel bleed in patients with early in-hospital rebleeding. By analyzing their published data, we found a significantly increased (2.3-fold; P = 0.016) relative risk (OR, 2.5) of rebleeding in patients with a sentinel bleed compared with those without. In a study conducted by Fujii and coworkers concerning ultraearly rebleeding, as a definition for having had ‘rebleeding before admission,’ the authors used the same criteria as we and others have used for the presence of SH, which include clinical signs of SAH such as sudden headache or loss of consciousness within 2 weeks before admission. There was no diagnosis of SAH made at the time of the first event, so these criteria apply to SH. In a univariate analysis of their published data, with these patients having been regarded as those with an SH, one can find a statistically significant, increased (2.8-fold; P = 0.004) relative risk (OR, 3.8) of rebleeding in patients with an SH compared with those without. These relations as found by others support the importance of SH as a risk factor for rebleeding.

Conclusions
The main conclusion of this study is that the presence of an SH is strongly related to an increased frequency of rebleeding before aneurysm obliteration. By analyzing published data from other recent studies, we corroborated this association. This finding suggests a causal relation between SH and the intracranial aneurysm. Therefore, a history of SH might be used to identify a subgroup of patients with a high risk for rebleeding and who could benefit from ultraearly aneurysm obliteration or immediate clot-stabilizing drug treatment.

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Disclosures
None.

References
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