Outcome of aneurismal subarachnoid hemorrhage: How far is vasospasm involved? – Retrospective study

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Received 10 November 2014; accepted 6 December 2014
Available online 29 December 2014

Abstract  
Purpose: To evaluate vasospasm and/or other possible mechanisms as a contributor to poor outcome following aneurismal subarachnoid hemorrhage (SAH).

Materials and methods: Sixty patients with aneurismal SAH, and severe cerebral vasospasm warranting endovascular angioplasty were included. Data included age, sex, bleeding severity, number and territory of spastic arteries, angioplasty result, development of new infarcts and their location relative to spastic territory. Final outcome was reported.

Results: There was strong correlation between outcome and both grade of hemorrhage and age. Angioplasty was either successful (80%), equivocal (10%), failed (8.3%), or could not be done (1.7%).

New Infarcts were found in 44/60 patients (73.3%). In 7 of which (16%) they were out of spastic territory. The remaining 37 (84.1%) had infarcts anatomically related to spasm, of these, 28 had successful angioplasty (75%).

No new infarcts were found in the remaining 16 patients (26.7%). There was no significant correlation between new infarcts and either successful angioplasty or outcome. However, when outcome was correlated to infarcts within the spastic territory, it turned strongly significant ($p = 0.008$).

Conclusion: Vasospasm and new infarcts have different pathophysiology. Only the coexistence of both in the same territory significantly correlates with poor outcome. Both are related to severity of SAH.

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1. Introduction

In 1951, Ecker and Riemenschneider [1] published a small study of patients with subarachnoid hemorrhage (SAH), in which vasospasm was demonstrated angiographically, and
the connection between vasospasm and ischemia after SAH was established.

Earlier observations of the cortical surface revealed that electrical, chemical, and mechanical stimuli often caused arterial constriction [2] Echlin [3] demonstrated in 1942 that this induced vasospasm could in turn impair cerebral blood flow (CBF). In 1949, Robertson [4] investigated cerebral infarction after SAH, and was the first to speculate on arterial spasm as a possible cause.

In subsequent studies [5], researchers confirmed that angiographically demonstrated vasospasm is quite common after aneurysm rupture and is frequently associated with clinical evidence of cerebral ischemia. In 1965, Kagstrom et al. demonstrated that vasospasm is usually “delayed” for at least 3 days after the initial SAH. Other investigators have elaborated on the association and temporal relationship between angiographically demonstrated and “clinical” vasospasm [6–9]. Considerable effort over the years has gone into clarifying the pathogenesis, clinicopathological associations, and treatment of vasospasm.

More recently, several lines of evidence cast doubt on angiographically confirmed vasospasm as the sole cause of DINDs.

First, although large cerebral arteries contribute more to vascular resistance than do arteries elsewhere in the body, their contribution to the regulation of cerebral flow (CBF) is still relatively minor [10,11]. Marked constriction of large cerebral arteries can occur without a decrease in parenchymal CBF [12].

Second, there is poor correlation between the sites and severity of angiographically confirmed vasospasm and cerebral ischemia whether symptomatic [13,14] or measured [15,16]. Symptoms and findings of DINDs often follow peak vasospasm by several days. The presence and location of angiographically demonstrated vasospasm fail to correlate with areas of cerebral infarction in as many as one third of cases [17]. There are cases in which documented SAH-induced ischemia occurs without vasospasm [18,15,19], and it is possible to increase CBF in experimental vasospasm without reversing the spasm itself [20,21] Minhas et al. [22] performed simultaneous positron emission tomography and TCD ultrasonography studies in patients after SAH. They did not observe a correlation between the two, thereby “calling into question the traditional concept of large-vessel vasospasm.”

Third, autopsy studies performed in patients after SAH reveal that the majority of infarcts are widespread and scattered, small, wedge-shaped, or laminar [23–25]. This pattern is more consistent with small thromboembolic than with large arterial spasms. Stoltenberg-Didinger [26] who studied 156 patients who died and had not undergone surgery, found that 76% had evidence of small infarcts. In contrast, fewer than 6% had large, territorial lesions [27]. These small infaracts were often located immediately beneath the thickest subarachnoid clots. These findings and others prompted Neil-Dwyer and colleagues [28] to suggest diffuse microangiopathy as the major cause of DINDs after aneurysmal SAH.

Fourth, in clinical practice there are several effective therapies that are used to combat angiographically demonstrated vasospasm. However, these treatments had less of an effect on infarct burden or patient outcome [29–33] (see Figs. 1–3).

Treatments such as intracisternal implantation of nicardipine pellets after SAH can reduce angiographically confirmed vasospasm but do not affect DINDs [34].

In some studies investigators suggest that endovascular treatment of aneurysms is associated with less frequent and less severe angiographically demonstrated vasospasm than surgical occlusion. However, this has occurred without a corresponding improvement in outcome [35]. Finally, transluminal angioplasty and intraarterial papaverine administration are effective in reversing angiographically demonstrated vasospasm. Nevertheless, their effect on patient outcome is less certain [36].

An alternative theory for DINDs is the possibility that blood or its breakdown products are directly neurotoxic. However, in animal models of SAH [37–40] and models that involve exposure to blood products, [41] ischemia invariably precedes necrosis.

The aim of this work was to investigate how consistent is vasospasm as a mechanism of delayed ischemic neurological deficit (DIND), and whether there are other possible mechanisms that may contribute to delayed ischemia and/or poor outcome, following aneurysmal SAH.

2. Materials and methods

We have retrospectively reviewed the files of patients who have been admitted to Nasser Institute Hospital, during the period from 2006 to 2012, with CT-proven aneurismal subarachnoid hemorrhage (SAH), and who had suffered severe cerebral vasospasm warranting endovascular intervention by angioplasty. Patients with asymptomatic vasospasm and those with symptomatic vasospasm that responded to medical treatment have been excluded from the study cohort. Follow-up CT scan was done for every patient at least once after angioplasty (prior to discharge), and earlier whenever there was remarkable alteration in the neurological status of the patient. If the CT study was done less than 48 h of onset and showed negative result, then it was repeated after 48 h.
The data reviewed included age, sex, the severity of hemorrhage at CT, the territory and the number of spastic arteries at angiography, the technical result of angioplasty at the end of the procedure and the development of new infarcts at follow up CT scan as well as the location of such infarcts in relation to the spastic artery territory.

The clinical severity of SAH was graded according to the Hunt and Hess scale (from 1 to 5) [42]. The technical result of angioplasty was classified into either success (restored near-normal caliber and flow through the plastied territory, with no appreciable delay in comparison to non-affected territory) or failure.

The final outcome of the patient was reported in terms of modified Rankin scale (from 0 to 6) [43]. However, in order to get fewer groups with more data samples, it was corrected to 4 grade scale (from 0 to 3), where 0 = complete recovery, 1 = minor deficit not interfering with patient’s activities, 2 = moderate disability (needs assistance), and 3 = severe disability (needs nursing care) or death.

Data were verified and coded prior to analysis. All data were expressed as mean ± SD and frequencies for quantitative and qualitative data respectively. Chi-square test has been performed to evaluate the association between different qualitative variables. The analysis has been performed using the SPSS version 11.

3. Results

Sixty patients represented the cohort of this study, one third of which were males (20 patients, 33.3%), vs. 40 females, (66.7%). The range of age was 21–83 years (mean age = 49.2 ± 13.6). The grade of hemorrhage was not

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**Table 1** Distribution of grade of hemorrhage.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>8</td>
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<td>4</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Not known</td>
<td>9</td>
</tr>
</tbody>
</table>

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**Fig. 2** Left: Left vertebral angiogram showing vertebro-basilar junctional aneurysm (long arrow). Notice spastic left vertebral (short arrows) and right PCA origin (dotted arrow). Right: Follow up angiogram after coiling and angioplasty.

**Fig. 3** Left ICA angiogram showing spasm of distal left ICA (dotted arrow), MCA and – infantile – PCA. Both ACAs look markedly spastic (short arrows).
4. Discussion

All the patients included in this study had suffered severe vasospasm that is related to a preceding episode of SAH. The patients’ charts had shown that grading of vasospasm was based on clinical assessment of the patient’s Modified Rankin and/or Glasgow Coma Scales (GCS), in addition to transcranial Doppler (TCD) and cerebral angiography findings. We did not go deeply into the criteria for grading of vasospasm in each case, which is beyond the scope of this work, and we relied on the mere history that those patients had severe vasospasm that warrants further intervention by angioplasty.

Although all patients were classified as severe vasospasm, we have proposed the number of spastic arteries (as shown in cerebral angiography) as a possible further sub-grading for the severity of vasospasm.

The clinical grade of hemorrhage was assessed based on the Hunt and Hess scale rather than the Fisher’s scale [44]. In a number of cases, the grade of bleeding was mentioned as well according to Fisher’s scale, which is merely based on CT imaging. Since the assessment of vasospasm and follow up as well as the final outcome was mainly based on the clinical picture, we believed that the Hunt and Hess scale might be more suitable, hence we omitted Fisher’s grade.

The final patient’s outcome assessment was based on the modified Rankin scale. While the original scale is graded from 0 to 6, we believed that such 7-grades scale might result in many groups with fewer data samples, hence our decision to downscale the results into a 4-grade system. From a statistical point of view, this will help as we deal with fewer numbers of groups with more data samples.

The development of new infarcts at follow up CT scan is a crucial point in the context of this work. Our main effort was directed toward the establishment (or denial) of etiological relationship between the existing vasospasm and any newly developed infarct(s) as well as its contribution to the final clinical outcome, and whether such relationship is statistically significant or not.

The basic assumption that severe vasospasm would result in impaired blood flow to the affected territory with subsequent development of new infarct, has been tackled by many authors and could not be established [10–12]. In our study, although there was significant coincidence between the spastic territory and the location of the new infarcts, however, this assumption is not applicable, as it does not take into consideration the fact that the vasospasm has been interventionally reversed, with subsequent restoration of the normal – or near normal – vessel caliber. In other words, the spasm could be reversed but infarction could not be prevented, raising a question mark about the mechanism of development of those infarcts.
The development of new infarcts – per se – was not significantly related to the outcome. However, such relation between the development of new infarcts and the clinical outcome was strongly significant when these infarcts were located within the spastic territory. In other words, it is the co-existence of vasospasm and infarcts at the same territory that may contribute to the poor outcome, although both of them are not significantly related to each other. This finding is supported by a study of carotid artery stent placement [45], in which it has been confirmed that the combination of micro-emboli and impaired CBF produces more damage than either one alone. This may – possibly – raise the micro-embolic theory as a clue to answer the other question about those infarcts out of the spastic territory: how they developed, and why they do not contribute to outcome.

In addition, we have proposed that the more the number of spastic arteries, the more severe the ischemia and – subsequently – the worse the outcome should be. However we found that the clinical outcome had poorly correlated to the number of spastic arteries. This assumption/sub-classification of severity of vasospasm based on the number of spastic arteries could not be validated.

Fisher et al. [44] – and many others – had documented the correlation between grade of bleeding and the subsequent development/severity of vasospasm. In our current series, the grade of bleeding was significantly correlated to the clinical outcome. Stoltenberg-Didinger and Schwarz [27] found that 76% of their patients had small infarcts close to the thickest hematoma, vs. 6% who had large territorial infarcts, raising the possibility of microangiopathy and/or thrombo-embolic event, rather than large vessel spasm. Putting things together would mean that: while the grade of hemorrhage is significantly correlated to the severity of vasospasm as well as to the clinical outcome, however both of them are not significantly related to each other, but the coexistence of infarcts and spasm is. This would raise the possibility of associated micro-vascular and/or thrombo-embolic contribution in our series. Unfortunately, the size and shape of infarcts were not documented on the files in most of the cases.

We have found other supportive findings in the literature, as well. Peltonen et al. [46] had documented the rise of the coagulation markers in CSF and jugular venous blood shortly after SAH. Romano and coworkers [47] performed TCD monitoring of the middle cerebral artery for 30 min three times a week during the intensive care unit stay of 23 patients with ruptured aneurysms. Microembolic signals were detected in 70% of the patients and 32% of the insonated vessels. These findings support the suggestion that a large number of emboli, some of which may be causing symptomatic cerebral infarctions, occur after SAH.

Furthermore, the anti-coagulant effect of many successful DIND therapies may add support to the thrombo-embolic theory. This applies to many therapeutic lines such as protease inhibitors and hemodilution. Nimodipine, a Calcium channel blocker has been approved to improve the outcome in patients with SAH. However, there is no convincing evidence that nimodipine affects the incidence of either angiographic or symptomatic vasospasm, while its antiplatelet and fibrinolytic effects were documented [48,49].

5. Summary

The grade of SAH has been documented in the literature to significantly correlate with the severity of vasospasm. We have found significant correlation between grade of SAH and poor clinical outcome, however, both parameters (vasospasm and outcome) are not significantly related to each other. Moreover, the development of new infarcts has been noticed in many patients, again with no significant correlation to outcome, or to vasospasm. The presumed explanation is that vasospasm and new infarcts have different pathophysiology. We have found that it is the co-existence of both mechanisms in the same territory that correlates with the poor outcome. Both mechanisms – however – are related to the grade of the original SAH.

Conflict of interest

None declared.

References


