Complications after Angiogram-Negative Subarachnoid Haemorrhage: Comparative Study of Pretruncal and Nonpretruncal Hemorrhage Patients

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INTRODUCTION

According to subarachnoid blood distribution, angiogram-negative subarachnoid haemorrhage (SAH) can be divided into diffuse, focal and perimesencephalic. Recently, findings of improved neuroimaging studies have shown blood to be located in front of the pons rather than perimesencephalic, and suggested to rename perimesencephalic to pretruncal nonaneurysmal SAH (PNSAH) [1]. In the nonpretruncal nonaneurysmal SAH (NPNSAH), there are diffuse or focal patterns of bleeding.

Several studies [2, 3] have shown that SAH of unknown aetiology usually have mild clinical presentation and favourable outcome that is highly specific for PNSAH, which is also considered to be a benign condition [4, 5].

Favourable outcome implies a low incidence of SAH complications. Rebleeding is uncommon in PNSAH [6], and occurs as an exception [7]. If vasospasm happens, it is usually mild and focal, while diffuse and severe vasospasms are exceptions [4]. Acute hydrocephalus is often transient and complete recovery usually occurs [8]. As within global population of SAH patients, hyponatremia and cardiac problems may be encountered in these types of haemorrhage as well. PNSAH and NPNSAH have better outcome than aneurysmal one [3], but these two subgroups of angiogram-negative haemorrhages have different incidence of rebleeding and vasospasm – the complications of SAH which are the most common cause of morbidity and mortality [2, 9].

OBJECTIVE

The aim of this study was to analyse the complications in two forms of angiogram-negative spontaneous SAH: pretruncal (PNSAH) and nonpretruncal (NPNSAH).

METHODS

We examined 36 patients using CT scan within the initial 72 hours from bleeding, and after initial angiographic examinations they were separated into two groups: 18 patients with PNSAH and 18 patients with NPNSAH. The study was prospective.

In PNSAH, blood can be localized, but not necessarily, into the front part of ambient cisterns, and into the basal parts of the Sylvian fissure. There is no complete filling of the front interhemispheric fissure, with or without minimal filling of the lateral parts of the Sylvian fissure, with the lack of intraventricular blood [10, ...]
11], but small amounts of blood sediment in the occipital horns of the lateral ventricles is permissible [12]. Those angiogram-negative haemorrhages that did not fulfill the criteria mentioned above were named NPNSAH.

Initial four-vessel digital subtraction angiography (DSA) was performed in all patients and revealed no diagnostic findings. Repeat DSA performed in five PNSAH and all NPNSAH patients revealed aneurysms in two NPNSAH patients. They underwent surgery and were excluded from our study. Repeat DSA in the remaining patients was negative. Besides DSA, MRI was obtained in seven patients and no finding of operative importance was found.

Clinical data were obtained immediately by physical examination of patients or by reviewing medical records. Clinical status of the patients on admission was scored according to the Hunt-Hess Scale and Glasgow Coma Score (GCS). Radiological markers of complications, ECG and laboratory findings were taken from medical records. ECG findings suggestive of arrhythmia (sinus tachycardia, atrial or ventricular extrasystoles, bradycardia), or coronary insufficiency (inverted T-waves, Q-T prolongation, S-T segment elevation or depression, pathological Q-wave) were considered in statistical analysis. Patients with medical history of coronary disease or arrhythmia (4 and 3, respectively) were not considered in this analysis and exception were those with new ECG changes. After discharge, the patients were seen in the outpatient clinic, or interviewed by telephone.

Basic screening (coagulation) laboratory tests were performed in all of our patients: platelet count (reference values – r.v. 150–450×10^9/L), bleeding time for platelet function (Duke method; r.v. 1-3 min), activated partial thromboplastin time (aPTT; r.v. 24-35 s), International Normalized Ratio (INR; r.v. 0.8-1.2). In nine patients we performed specific factor assays, like thrombin time (TT; r.v. 15-20 s). Analyses of serum electrolyte were also performed: serum sodium (r.v. 135-148 mmol/l), potassium (r.v. 3.5-5.5 mmol/l) and calcium levels (r.v. 2.2-2.65 mmol/l). Also, glycemia (r.v. 3.9-6.1 mmol/l), blood cholesterol (<5.2 mmol/l) and lipid status (<2.3 mmol/l) were also checked.

The patients were followed up for 4 to 46 months (mean 21.3 months).

In our study the assessment of statistically significant differences was performed by Student’s t-test, Fisher’s or Mantel–Haenszel Chi square test.

RESULTS

There were 18 PNSAH and 16 NPNSAH patients in our study (Figure 1), 14 males and 20 females. In PNSAH patients, there were 10 males and 8 females. The age in PNSAH patients ranged from 21 to 74 (46.6±13.9) and in NPNSAH patients from 27 to 69 (49.9±12.1) years.

In five PNSAH patients (27.7%), CT findings showed complete filling of all perimesencephalic cisterns, which was not the case in the remaining 13 PNSAH patients.

Twenty-nine patients were in grade I or II of the Hunt-Hess scale (17 or 94.4% PNSAH and 12 or 75% NPNSAH). Only one PNSAH was in grade III, but three NPNSAH patients were in grade III and one in grade IV (Table 1).

Rebleeding occurred only in one female NPNSAH patient about a month after the initial haemorrhage. She was again hospitalized and repeat DSA showed no cause of rebleeding. After admission therapy, the patient was discharged in good condition.

In four PNSAH patients (22.2%) and in six NPNSAH patients (37.5%) acute hydrocephalus occurred (Table 1). Three of the four PNSAH patients that developed hydrocephalus had complete filling of all perimesencephalic cisterns. The severity of ventricular dilatation and clinical course of the patients gave no reasons for doing ventriculostomy in any of the cases. At the end of our study,
ECG changes presented as negative Q in one of the leads, but without enzyme or echocardiography verification of myocardial infarction. At the end of our study, all of the patients were alive.

As presented in Table 1, NPNSAH patients usually had a slightly severe clinical presentation, and higher prevalence of complications compared to PNSAH patients; however, statistical analysis revealed no significant differences with exception of ECG changes (p=0.037; p<0.05). In addition, there were no significant differences in the presence of risk factors in PNSAH and NPNSAH patients (Table 2), although a trend toward less smoking (p=0.097) and less likely to be a female (p=0.075) in PNSAH patients was visible.

**DISCUSSION**

The most common cause (75-80%) of spontaneous subarachnoid haemorrhage is aneurysm rupture. The second most frequent cause (4-5%) is bleeding from arterio-venous malformations [13]. However, the cause of SAH cannot be identified in 15-24% [14, 15]. PNSAH is found in 50-75% of patients with angiogram-negative SAH [12].

Various causes of angiogram-negative SAH have been proposed: cerebral or spinal vascular malformation, vasculitides, tumour of the brain or spine, infections, blood dyscrasias, venous or sinus thrombosis, consumption of some drugs or nonvisualised aneurysms. Aetiology of PNSAH is the subject of discussion, because some authors find venous [16] and some arterial [5] origin of PNSAH.

In 5% to 10%, a typical PNSAH finding on the initial brain CT is the result of posterior circulation aneurysm rupture, so that some aetiological doubts must remain until angiography findings eventually eliminate aneurysmal cause of bleeding [3, 17, 18, 19].

It must not be forgotten that angiography carries 0.07-0.50% risk of permanent neurological deficit [12, 20]. Most experts agree that repeat angiography is not indicated in patients meeting the criteria of PNSAH [15, 21, 22]. However, there is another group of authors [23] who disagrees with the previous one. According to the third group of authors [24], the most beneficial option for patients with a perimesencephalic pattern of haemorrhage on CT is CT angiography only.

In SAH patients, repeat angiography is indicated in cases of incomplete visualization of all cerebral blood vessels on the initial four-vessel angiogram, vasospasm, dislocation of cerebral arteries, suspicious findings, and depending on subarachnoid blood distribution on CT, in all cases of diffuse and focal SAH [15].

Commonly, PNSAH appears in the middle-aged patients, aged around 50 years [12], although cases of paediatric PNSAH are well known [25]. In some studies [7, 26], all of the PNSAH patients were in grade II or I, in others the impairment of consciousness was reported, but very rarely [2, 27].

In 22% of PNSAH patients acute hydrocephalus occurred, which is a slightly lower percentage than in the study.

### Table 1. Assessment of statistically significant differences in the appearance of complications and clinical status in PNSAH and NPNSAH patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>PNSAH</th>
<th>NPNSAH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS&lt;12 on admission</td>
<td>0 (0%)</td>
<td>1 (6.25%)</td>
<td>0.470</td>
</tr>
<tr>
<td>Grades III and IV of the Hunt-Hess Scale</td>
<td>1 (5.6%)</td>
<td>4 (25%)</td>
<td>0.164</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>4 (22.2%)</td>
<td>6 (37.5%)</td>
<td>0.457</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>-</td>
<td>1 (6.25%)</td>
<td>0.470</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>2</td>
<td>2 (12.5%)</td>
<td>0.213</td>
</tr>
<tr>
<td>Acute ECG changes</td>
<td>7 (38.9%)</td>
<td>12 (75%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>9 (50%)</td>
<td>11 (68.8%)</td>
<td>0.268</td>
</tr>
<tr>
<td>Working inability</td>
<td>3 (16.6%)</td>
<td>4 (25%)</td>
<td>0.682</td>
</tr>
</tbody>
</table>

### Table 2. Assessment of statistically significant differences in the presence of risk factors in PNSAH and NPNSAH patients

<table>
<thead>
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<th>Variable</th>
<th>PNSAH</th>
<th>NPNSAH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>46.6</td>
<td>49.9</td>
<td>0.112</td>
</tr>
<tr>
<td>Male gender</td>
<td>10 (55.5%)</td>
<td>4 (25.00%)</td>
<td>0.075</td>
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<tr>
<td>Chronic coronary disease</td>
<td>2 (11.11%)</td>
<td>2 (12.55%)</td>
<td>0.999</td>
</tr>
<tr>
<td>History of arterial hypertension</td>
<td>4 (22.22%)</td>
<td>6 (37.5%)</td>
<td>0.457</td>
</tr>
<tr>
<td>Chronic coronary dysrhythmia</td>
<td>1 (5.55%)</td>
<td>2 (12.55%)</td>
<td>0.591</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (27.77%)</td>
<td>9 (56.25%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (38.88%)</td>
<td>10 (62.50%)</td>
<td>0.175</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>5 (27.77%)</td>
<td>6 (37.5%)</td>
<td>0.551</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>1 (5.55%)</td>
<td>2 (12.55%)</td>
<td>0.591</td>
</tr>
<tr>
<td>Body Mass Index &gt;30 kg/m²</td>
<td>0 (0%)</td>
<td>2 (12.55%)</td>
<td>0.214</td>
</tr>
</tbody>
</table>
of Rinkel et al. [28] (27.5%). These authors found a statistically significant correlation between complete filling of all perimesencephalic cisterns and hydrocephalus occurrence. The presence of blood in the basal cisterns is a major block of the cerebro-spinal fluid (CSF) circulation in the tentorial hiatus region, and therefore the direct cause of ventricular dilatation [28]. However, the size of ventricles, amount of blood in the rest of subarachnoid space, natural route of CSF, can also be important in hydrocephalus genesis. This is an explanation of a higher incidence of ventricular dilatation in NPNSAH patients compared to PNSAH ones.

Cerebral vasospasm (CVS) is not typical of PNSAH patients; however, some authors describe diffuse and severe forms of this complication [4, 2]. This is of great importance because CVS is the most significant cause of morbidity and mortality in patients surviving SAH long enough to reach medical care [13]. Knowing the fact that maximal frequency of CVS onset is between the 6th and 8th day after SAH, and that it usually resolves over 3-4 weeks [22], we performed repeat angiographies in both CVS cases after 22 days and found complete resolving. A sufficient amount of blood located at specific sites is the most important factor in CVS pathogenesis. Almost all severe CVS patients consequently develop signs of brain ischemia of the areas irrigated by spastic arteries [29].

Annual risk of rebleeding in angiogram-negative SAH patients is 0.5% [13]. There was no single case of rehaemorrhage in the PNSAH patients in our study, similar to the studies performed by Rinkel et al. [6], or by Barth et al. [26]. Nevertheless, there are some case reports of rehaemorrhages in PNSAH patients after 30 months [7]. According to Roos et al. [30], in 34% the major causes of unfavourable outcome in SAH patients are the effects of initial rebleeding.

Morphologic ECG changes occur in 50-90% of SAH patients [31]. In our study, 39% of PNSAH and 75% of NPNSAH patients had newly abnormal ECG findings, which is rather high considering the benign character of these types of SAH. We found a significantly higher frequency of ECG abnormalities in the NPNSAH patients compared to PNSAH ones (p=0.037; p<0.05). The most common findings are broad or inverted T-waves, Q-T prolongation, S-T segment elevation or depression [32]. ECG abnormalities after SAH are hard to distinguish from acute coronary syndrome, and sometimes are interpreted in such way. Pathological Q wave can be found, but it is transient like S-T segment elevation or depression [33], or broad or inverted T-waves, and can persist as long as eight weeks [34]. Except for morphological ECG changes, arrhythmias can be found in more than 75% of SAH patients, usually tachyarrhythmias and bradycardias [35]. Most of them are benign, like sinus tachycardias, atrial or ventricular extrasystoles. Our results showed a lower frequency of rhythm disorders than in the general SAH population. In two cases with pathologic Q in one lead only there was neither enzyme verification of myocardial necrosis nor ultra sound dysfunction of the myocardium. The finding of pathologic Q in less than two linked leads is not pathognomonic for myocardial necrosis, and could have transient characteristic. All of the patients that developed cardiac problems did so in the acute phase of SAH, and therefore cardiac monitoring is necessary starting from admission until signs of improvement appear.

In genesis of cardiac problems following SAH, the activation of sympathetic nervous system plays the major role, therefore increasing the level of catecholamines. Catecholamine releasing is connected to myocardial necrosis and increased levels of cardiac-specific enzymes, and very high levels of troponin I imply severe myocardial damage. Probably, catecholamines have a direct toxic effect on myocardiocytes or provoke coronary vasoconstriction and the consequent myocardial lesion [36].

Even minimal pretruncal SAH is a stressful event, which through stress hormones-releasing catecholamines, cause intensive glucagon release and glucose mobilization. This explains that the most common finding in our study was hyperglycemia in nine PNSAH and 11 NPNSAH patients including patients in each group with history of diabetes mellitus.

Hyponatremia frequently follows SAH, as the result of natriuresis and diuresis. This is caused by the intensive atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP) secretion, and results in hypovolemia. Nevertheless, in our study, only one patient had hyponatremia, which explains the fact that none of our patients had cerebral infarction that is three times more often after SAH in hyponatremic than in normonatremic patients [37]. But, far more often the values of serum potassium were above normal, in seven PNSAH and eight NPNSAH patients, and ranged from 3.4 to 4.0 mmol/L. It seems that electrolyte disbalance in angiogram-negative SAH patients differs from usually intensive and severe aneurismal haemorrhage, which triggers more intensive ANF and BNP releasing.

The variations documented in a study of Flaherty et al. [38] suggest fundamental differences in the risk factor profile and aetiology of PMSAH and aneurismal SAH. Compared to all other SAH patients, those with PNSAH were younger and less likely to be female or hypertensive with a trend toward less smoking. Nevertheless, these authors did not undertake the regression analysis when comparing PNSAH and NPNSAH cases. In our study, we found no significant correlation between the type of SAH and risk factors, although the trend toward less smoking (p=0.097) and male gender (p=0.075) in PNSAH patients was obvious. Our study and the performed investigation of the influence of the risk factors on complication appearance were limited by small numbers. For this reason, we did not undertake a multivariate statistical analysis to compare the cases of complicated PNSAH (or NPNSAH) with the presence of risk factors to those without it.

The patients from both groups generally had a good recovery, contrary to the aneurismal SAH [39].
CONCLUSION

PNSAH and NPNSAH are two distinctive types of bleeding, both with favourable outcome. Results of our study show a more frequent occurrence of complications in NPNSAH compared to PNSAH patients, but without statistical significance, with the exception of ECG changes. Cardiac problems following these types of SAH are more frequent than expected, and therefore cardiac monitoring is necessary.

REFERENCES

Комплексије након ангиограм-негативне субарахноидне хеморагије: компаративна студија болесника с претручупкским и непретручупкским крварењем

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КРАТАК САДРЖАЈ
Увод Субарахноидне хеморагије (SAX) непознатог узрока обично имају благу клиничку слику, повољан исход и нишу стопу компликација.
Циљ рада Циљ рада био је да се анализишу компликације два типа ангиограм-негативних спонтаних субарахноидних крварења – претручупкских (PNSAH) и непретручупкских (NPNSAH).
Методе рада Испитано је 18 болесника с PNSAH и 16 болесника с NPNSAH. CT снимак мозга је начињен у прва 72 сата од крварења. Сви болесницима је урађена церебрална ангиографија сва четири крвна суда. Поновна ангиографија је урађена код пет испитаника с PNSAH и свих болесника с NPNSAH.
Резултати Према Хант-Хесовој (Hunt–Hess) сказали за клизики фиковање SAX, код 17 болесника са PNSAH и 12 са NPNSAH утврђен је I или II степен обољења. Код једног болесника са NPNSAH догодило се поновно крварење, док је код четири испитаника са PNSAH и шест са NPNSAH установљен пролазни хидроцефалус. Церебрални вазоспазам уочен на ангиограмима два болесника са NPNSAH био је локалног типа и благ, док у групи испитаника са PNSAH није забележен. Електрокардиографске измене у акутној фази биле су значајно чешће код болесника са NPNSAH него са PNSAH (12 према 7; p=0,037).
Закључак Проблеми са срцем након ових типова SAX чешћи су него што би се очекивало, па је још и кардиолошки надзор болесника неопходан.
Кључне речи: ангиограм-негативна субарахноидна хеморагија; комплекције; електрокардиографија

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