ABSTRACT

AIM: The purpose of this study was to compare the different clinical features, outcome and treatment strategies in patients with perimesencephalic SAH (p-SAH) and diffuse SAH (d-SAH).

MATERIAL and METHODS: 83 patients with spontaneous SAH and negative initial cerebral angiography were retrospectively reviewed.

RESULTS: There were 49 patients with p-SAH and 34 with d-SAH. The patients with d-SAH were likely to be hypertensive and smoking and have elevated cholesterol and lactate dehydrogenase and White blood cells. 95.9% of patients with p-SAH had a Hunt&Hess grade of I-II, whereas 73.5% of patients with d-SAH had Grade I-II, 9 patients had Grade III-IV. All patients with p-SAH had a modified Fisher scale of 1-2 and a favorable outcome, whereas 47 % and 8.8% of the patients with d-SAH had a score of 1-2 and had a poor prognosis, respectively. Hydrocephalus, clinical vasospasm, re-bleeding and pneumonia were common in patients with d-SAH.

CONCLUSION: The initial bleeding pattern was associated with the initial clinical condition and outcome, and d-SAH might lead to a worse clinical course and outcome and might have a high risk of complications. Repeated DSA is recommended to exclude aneurysm in patients with d-SAH, whereas CT angiography was enough in patients with p-SAH.

KEYWORDS: Perimesencephalic subarachnoid hemorrhage, Subarachnoid hemorrhage of unknown origin, Computerized tomography angiography, Negative angiography

Different Clinical Characteristics Between Perimesencephalic Subarachnoid Hemorrhage and Diffuse Subarachnoid Hemorrhage with Negative Initial Angiography

Negatif Başlangıç Anjiyografili Perimezensefalik Subaraknoid Kanama ve Difüz Subaraknoid Kanamanın Farklı Klinik Özellikleri

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ABSTRACT

AMAÇ: Bu çalışmanın amacı, perimezensefalik SAK (p-SAK) ve difüz SAK (d-SAK) hastalarında farklı klinik özellikler, sonuç ve tedavi stratejilerini karşılaştırmaktır.

YÖNTEM ve GEREÇLER: Spontan SAK ve negatif başlangıç serebral anjiyografisi olan 83 hasta retrospektif olarak değerlendirildi.

BULGULAR: 49 p-SAK ve 34 d-SAK hastası vardı. d-SAK hastalarının hipertansif olması, sigara içmesi, kolesterol, LDH ve akyuvar düzeylerinin daha yüksek olması, HH grade I-II'ye kadar bulunan %85,9'a kadar H&H sınıf I-II iken, d-SAK hastalarının %73,5, sınıf I-II'ye kadar bulunan %9, saniye Fisher 1-2 olan p-SAK hastalarının tümünde sonuç olumluudur ama puanın 1-2 olduğu d-SAK hastalarının rassıla %47'si ve %8,8'inde прогноз iyi deyildi. Hidrosefali, klinik vazosporaz, tekrar kanama ve pnömoni d-SAK hastalarında daha sıktı.

SONUC: Başlangıç kanama paterni, başlangıç klinik durum ve sonucu ilişkilidi ve d-SAK daha kötü bir klinik seyir ve sonucu neden olabilir ve komplikasyon riski de daha yüksek olabilir. d-SAK hastalarında anevrizmayı ekarte etmek için DSA tekrarı öneriliken, p-SAK hastalarında BT anjiyografisi yeterliydi.

ANAHTAR SÖZÜKLERİ: Perimezensefalik subaraknoid kanama, Bilinmeyen nedenli subaraknoid kanama, Bilgisayarlı tomografi anjiyografi, Negatif anjiyografi
INTRODUCTION

The incidence of spontaneous subarachnoid hemorrhage (SAH) with unknown origin on initial digital subtraction angiography (DSA) (20) is about 10-20%, and can be divided into two main subgroups: perimesencephalic SAH (p-SAH) and diffuse SAH (d-SAH). The hemorrhage of the former is only located within perimesencephalic cistern and the latter could involve multiple cisterns (19). Their origins, clinical course and outcome might be different, so treatment strategies are not identical. Herein we retrospectively reviewed the clinical characteristics of patients with spontaneous SAH and negative initial cerebral angiography (DSA) to compare the different clinical features, outcome and treatment strategies between patients with p-SAH and patients with d-SAH.

MATERIAL and METHODS

83 patients (42 male, 41 female; age range: 26–76 years, mean age: 53.4 years) with spontaneous SAH and negative initial cerebral angiography treated in our department from January 2009 to February 2012 were included in this study, and these patients accounted for about 16% of all patients with spontaneous SAH in our department during that period. The hemorrhages were all confirmed by head computerized tomography (CT) scan and the patients with an initial CT scan performed > 24 hours of the first symptoms were excluded. The SAH patterns were classified into two groups: p-SAH and d-SAH. The definition of p-SAH was based on Rinkel et al., (19): 1) center of the hemorrhage located immediately anterior to the midbrain or brainstem, 2) possible extension of blood to the anterior part of the ambient cistern or to the basal part of the sylvian fissure; 3) no complete filling of the anterior interhemispheric fissure and no extension to the lateral sylvian fissure, except for minute amounts of blood; 4) absence of frank intraventricular hemorrhage, except for minute amounts of blood, and 5) absence of intracerebral hematoma. Hemorrhage within quadrigeminal cistern or ambient cistern was also considered as p-SAH (22) (Figure 1A-C). The latter was referred to hemorrhage involving multiple cisterns, such as Sylvian, suprasellar, interhemispheric and perimesencephalic cisterns. All patients underwent standard monitoring and received the same medical treatment for aneurysm SAH after admission. Multi-slice spiral CT angiography (CTA) was performed to evaluate the cause of hemorrhage before/after negative initial DSA. The patients were followed up via outpatient clinic or by telephone interview, with an average time of 7 months (range: 4–46 months). Their demographic, clinical and radiological features, laboratory findings and outcome were clearly reviewed. The blood tests were carried out in emergency department within one hour after admission, including total white blood cell (WBC) count, neutrophil ratio (N%), blood glucose (Glu), fibrinogen (Fib), triglycerides (TG), cholesterol (CHOL), low density lipoprotein (LDH) and high density lipoprotein (HDH). The initial neurological conditions were evaluated using the Hunt and Hess grading system (H&H), and were divided into two groups (mild: H&H 1-3; serious: H&H 4-5). The amount of subarachnoid blood was classified by the modified Fisher scale MFS (3). The outcome was assessed according to the Glasgow Outcome Scale (GOS) and was divided into two groups (favorable outcome: GOS 4-5, poor outcome: GOS 1-3). Appropriate statistical tests including Fisher’s exact test, Chi-squared (x2) test or Student’s t-test were used. Values of \( P < 0.05 \) were considered as statistically significant, and \( P \) values between 0.05 and 0.10 were considered to be a trend between them.

RESULTS

The demographics of these patients are available in Table I. There were 49 (59%) patients with p-SAH and 34 (41%) with d-SAH, the sex and age distribution was similar in each group. The patients in the d-SAH group were more likely to present a history of hypertension (\( p=0.001 \)) and smoking (\( p=0.028 \)), and the serum CHOL, LDH and WBC were significantly higher in the d-SAH group (\( P_c=0.001, P_l=0.000, P_w=0.039 \)), similar

Figure 1: A) CT scan showed a typical p-SAH located within prepontine and left ambient cisterns, B, C) showed a rare type of perimesencephalic hemorrhage located within the quadrigeminal and ambient cisterns.
trends in TG, HDL and Fib were also noted in d-SAH group, but their differences were not significant whereas precipitating factors such as manual working and dancing were more frequently noticed in the p-SAH group (16.3%) than the d-SAH group (8.8%), as shown in Table I.

The most common symptoms were headache and vomiting, similar in each group (Table II). However, the initial neurological condition was much more serious in the d-SAH group (Table III), focal neurological deficits were frequently noticed in the d-SAH group, and these patients usually had long-term hospitalization (p=0.02). Furthermore, the initial CT scan usually showed much more bleeding in d-SAH group (p=0.000), all patients with p-SAH had a MFS of 1-2 whereas 21.7% patients with d-SAH had a grade of 3-4.

In the last follow-up, 8 patients with p-SAH underwent repeated four-vessel angiography and 45 patients underwent CT angiography and of these, 23 patients underwent repeated CT angiography. None of them showed aneurysm or re-bleeding. In the d-SAH group, 27 of 34 patients underwent repeated four-vessel angiography, 20 patients underwent CT angiography and of these. 6 patients had repeated CT angiography, cerebral aneurysms were revealed in 4 patients (11.8%) as the cause of initial hemorrhage within 7 to 12 days after hemorrhage. Two of them were anterior communicating artery aneurysm, one was a paraclinoidal aneurysm, and the other one was anterior inferior cerebellar artery aneurysm. All were confirmed by repeated cerebral angiography, and one of them was also revealed on CT angiography.

SAH-related complications are presented in Table IV. These were more frequent in the d-SAH group (p=0.04) or patients with serious neurological condition (p=0.03). The most common complication was acute hydrocephalus that required shunting, which occurred in 5 patients with d-SAH and one with p-SAH, only two of them required persistent shunting in the d-SAH group (p=0.04). 4 cases with d-SAH and one with p-SAH also experienced clinical cerebral vasospasm (Figure 2A-D), which tend to occur in patients with a worse initial neurological condition and a MFS of 3-4. Although it

Table I: The Demographics of Patients with Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Symptom and sign</th>
<th>p-SAH (n=49)</th>
<th>d-SAH (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(y), mean range</td>
<td>54.04±11.3 (26-76)</td>
<td>53.18 ±11.07 (28-75)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>24/25</td>
<td>18/16</td>
</tr>
<tr>
<td>Hospital stay, mean* range</td>
<td>7.4 (3-18)</td>
<td>10.6 (4-33)</td>
</tr>
<tr>
<td>Drinking</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Current smoking*</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hypertensive*</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.30±0.55</td>
<td>1.39±0.64</td>
</tr>
<tr>
<td>CHOL (mmol/L)*</td>
<td>4.15±0.63</td>
<td>4.85±0.99</td>
</tr>
<tr>
<td>LDL (mmol/L)*</td>
<td>2.44±0.57</td>
<td>3.01±0.84</td>
</tr>
<tr>
<td>HDL (mmol/L)*</td>
<td>1.29±0.29</td>
<td>1.48±0.47</td>
</tr>
<tr>
<td>HB</td>
<td>132.39±13.82</td>
<td>135.79±14.08</td>
</tr>
<tr>
<td>WBC*</td>
<td>9.48±3.29</td>
<td>11.65±5.00</td>
</tr>
<tr>
<td>N%</td>
<td>78.95±11.89</td>
<td>81.21±11.31</td>
</tr>
<tr>
<td>Fibrin</td>
<td>2.95±0.91</td>
<td>3.30±0.98</td>
</tr>
</tbody>
</table>

* indicates a significant difference between p-SAH and d-SAH, with a p value <0.05.
was not significant, re-bleeding was only noted in the d-SAH group \((p=0.065)\), which was significantly associated with a poor outcome, all that occurred within 7–12 days after the initial hemorrhage, and the aneurysm was only revealed in 2 of them. Other clinical complications such as pulmonary infections, new epilepsy and electrolyte disturbance were also only noted in d-SAH. The outcome tended to be worse in patients with d-SAH \((p=0.065)\) (Table III), all patients with p-SAH had a favorable outcome, whereas only 91.2% patients with d-SAH had a favorable outcome. The overall mortality rate was 1.2%, and only one patient in d-SAH group died of re-bleeding after hospital discharge.

**DISCUSSION**

Although the majority of spontaneous SAH is caused by ruptured intracranial aneurysm, there is still about 10-20% of spontaneous SAH with unknown origin \((20)\). p-SAH represents approximately 5% of all SAH and accounts for about 21-68% of all spontaneous SAH with unknown origin \((2, 9, 16)\). It usually occurs in middle-aged patients and is less likely to be female, hypertensive, smoking and hyperlipidemia as revealed in our study. The origin of the hemorrhage was still unclear, it has reported that the perimesencephalic SAH had a higher incidence of a primitive venous drainage in which the basal vein of Rosenthal was directly draining into the dura.

**Table IV**: Incidence of Complication in Patient with Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Complication</th>
<th>p-SAH</th>
<th>d-SAH</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical vasospasm</td>
<td>1</td>
<td>4</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Hydrocephalus required shunting</td>
<td>1</td>
<td>5</td>
<td>6 (7.2%)</td>
</tr>
<tr>
<td>Re-bleeding</td>
<td>0</td>
<td>4</td>
<td>4 (4.8%)</td>
</tr>
<tr>
<td>New seizure</td>
<td>0</td>
<td>1</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>1</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>4</td>
<td>4 (4.8%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>1</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>0</td>
<td>3</td>
<td>3 (3.6%)</td>
</tr>
</tbody>
</table>

**Figure 2**: A, B) CT scan showed p-SAH located in anterior to the midbrain and medulla, C, D) showed cerebellar infarction 3 day after negative DSA.
venous other than the vein of Galen venous system (1,28), and the hemorrhage was always on the side of the primitive drainage (24). Meanwhile, cavernous sinus thrombosis, venous sinus stenosis and jugular venous occlusion were also noticed in perimesencephalic SAH (10, 21, 23), so venous origin tend to be the most likely cause. Furthermore vigorous physical activities were frequently noticed in p-SAH patient as in our study, which were presumed to elevate intracranial venous pressure and promote venous rupture (16, 28). There were also some clinical features supporting venous origin of p-SAH: localized SAH, slower onset of headache, benign clinical course with infrequent loss of consciousness and favorable outcome (7, 12). Other rare potential contributing factors including hemorrhage from perforating arteries (11), intramural basilar arterial dissection (15), capillary telangiectasia (26), cavernous malformations (27) and tiny aneurysm (17) were also reported, but these are rare. The source of non-aneurysm d-SAH was even mysterious, but it tended to be of arterial origin because of its hemorrhage pattern and serious clinical course, similar to aneurysm SAH.

The symptoms in those patients include headache and vomiting, similar to that of aneurysm SAH, however, different initial bleeding patterns usually lead to different clinical conditions and outcomes. The clinical course of p-SAH was usually uneventful and the onset of headache was more gradual, neurological examination was usual normal except meningeal irritation and occasional drowsiness, their Hunt and Hess Grade tends to be I-II and the amount of p-SAH was much less with the modified Fisher scale ≤ 2, and they usually have an excellent outcome and a normal life expectancy (4). In this study, though complications such as vasospasm and hydrocephalus were also noted in p-SAH patients, all of them also experienced an excellent outcome. In contrast, the patients with d-SAH were frequently exposed to hypertension, smoking and hyperlipidemia, the bleeding pattern was similar to aneurysm SAH, the inflammatory stress response and damage to cerebral vascular and brain were much severe, so the neurological condition could vary from mild to severe. Loss of consciousness, severe neurological deficits and SAH-related complications were much common in those patients (13), which could result in a long-term hospitalization and a poor outcome. Patients with d-SAH rather than patients with p-SAH should therefore be closely monitored and should receive the same medical treatment for aneurysmal SAH, series head CT scan should be performed to early detect SAH-related complications.

With the advance in imaging technology, the sensitivity and specificity of CT angiography for diagnosing intracranial aneurysms has been increased, up to 98% and 100% respectively (25), CT angiography is costless and noninvasive, and could be performed safely and quickly, even in patients with inability to collaborate, furthermore, it could not cause painful and unpleasant memories (5), CT angiography is now even used as the only diagnostic technique for cerebral aneurysms, and the sole technique to exclude aneurysm in patients with classic p-SAH (5, 8). Our study also supported that the chance of harboring an aneurysm was smart in patients with classic p-SAH and CT angiography was enough to exclude aneurysm in those patients. However, some clinical criteria should be considered: strict diagnostic criteria of p-SAH should be carried out and the initial head CT scan should be performed earlier, multi-slice CT angiography should be available and should interpreted by an experienced neuroradiologist. The incidence of detected aneurysms through repeat angiography was about 10% to 17.5% in patients with d-SAH (14), with an incidence of 11.8% in our study. This may due to vascular vasospasm and thrombosis, so to avoid misdiagnosis and potential aneurysm rupture, the benefits of cerebral angiography might outweigh its risks in those patients. Repeated cerebral angiography is now still the best choice to exclude aneurysm in patients with diffuse SAH. The patients should be closely monitored and repeated angiography should be done within approximately two weeks after hemorrhage (6, 7). Though the MRI examination might found other rare bleeding sources in patients with p-SAH, MRI examination was not routinely performed for p-SAH in our study as the cost of MRI probably outweighs its benefit, and MRI examination may brought no additional benefit for detecting non-aneurysmal bleeding sources and had no influence for the performed therapy (18).

In conclusion, the initial bleeding pattern was strongly associated with the initial clinical condition and outcome. The patients with d-SAH tend to be serious in neurological condition and prognosis, and should be closely monitored and receive the same medical treatment for aneurysmal SAH. Repeated cerebral angiography is recommended in patients with normal initial angiography, however, multi–detector row CT angiography was enough to exclude aneurysm in patient with classical p-SAH.

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