Clinical characteristics of patients with pseudo-subarachnoid haemorrhage who were successfully resuscitated from out-of-hospital cardiopulmonary arrest

從院前心肺功能停頓中成功救活的假蛛網膜下出血病人之臨床特徵

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Introduction: Pseudo-subarachnoid haemorrhage (PSAH) is a rare neuroradiological finding seen in patients with diffuse cerebral edemas. We investigated clinical characteristics and risk factors for the development of PSAH. ***Method:*** The successfully resuscitated patients in emergency department were classified into two groups: those with pseudo-SAH [PSAH (+)] and those without pseudo-SAH [PSAH (-)]. Clinical variables were analysed. ***Results:*** Pseudo-SAH was found in 31.6% of patients. PSAH was more common in males (p=0.042). The mean age was 39.9±10.3 years in the PSAH (+) group and 54.4±22.0 years in the PSAH (-) group (p=0.038). Outcomes measured by Cerebral Performance Category score were also significantly different between the two groups (p=0.037). Logistic regression analysis found that serum lactate concentration and duration of anoxia were associated with the development of PSAH (with odds ratios and p values of 1.92, p=0.01 and 1.13, p=0.02, respectively). ***Conclusions:*** PSAH itself is a phenomenon that could be seen in post-resuscitation encephalopathy as a consequence of severe anoxic insult. (Hong Kong j.emerg.med. 2012; 19:85-91)

介紹：假蛛網膜下出血（PSAH）是一種在患有彌散性腦水腫病人身上罕見的神經系放射學檢定結果。我們研究了假蛛網膜下出血的臨床特徵和致病的危險因素。**方法：**在急症室內成功救活的病人被分為兩組：假蛛網膜下出血組[PSAH(+)]和沒有假蛛網膜下出血組[PSAH(-)]。臨床的變量得到分析。**結果：**在31.6% 的病人中檢定出假蛛網膜下出血，並以男性居多（p=0.042）。PSAH(+)組患者的平均年齡為39.9±10.3 歲，而 PSAH(-)組為 54.4±22.0 歲（p=0.038）。根據腦功能分級得分作出的評估結果在兩組中有顯著差別（p=0.037）。邏輯回歸分析顯示血清中乳酸鹽的濃度和缺氧的時間與 PSAH 的出現有關連（比數比和 p 值分別為 1.92, p=0.01 和 1.13, p=0.02）。**結論：**PSAH 本身是一個可能在復甦後因嚴重缺氧而導致的腦病中觀察到的現象。

Keywords: Anoxic encephalopathy, out-of-hospital cardiac arrest, subarachnoid hemorrhage

關鍵詞：缺氧性腦病、院前心肺功能停頓、蛛網膜下出血

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Introduction

Pseudo-subarachnoid haemorrhage (PSAH) is a rare finding. It is observed in areas of increased attenuation along the basal cisterns, the Sylvian fissure, the tentorium cerebella, or cortical sulci, and it mimics subarachnoid haemorrhage (SAH) on brain computed

tomography (CT) without subarachnoid blood.[1-4] This finding has been observed in various situations, including severe brain oedema, pyogenic leptomeningitis, and intrathecally administered contrast material.[5-9] However, the incidence and clinical significance of PSAH have not been elucidated because of its rarity. Although statistical analysis of the relationship between a finding of PSAH and a patient's prognosis has not been conducted thoroughly, several studies have reported that patients with PSAH have a poor prognosis,[8-12] and only one study has shown that patients with PSAH have a statistically significant poor prognosis compared to patients without PSAH.[4] Still, it is unclear why patients with PSAH have a poor prognosis relative to patients without PSAH. To the best of our knowledge, no study has yet analysed the factors associated with the development of PSAH.

We investigated clinical characteristics of patients with PSAH who were successfully resuscitated from out-of-hospital cardiopulmonary arrest (CPA), focusing on probable pathophysiology and risk factors for the development of PSAH.

Method

This study was retrospective in its design, reviewed consecutive CPA cases. This study protocol was reviewed and approved by institutional review board of our institute.

This study was conducted over 24 months from January 2008 to December 2009. Our hospital is a teaching hospital that is capable of performing tertiary care and is located within an urban area. To meet the enrollment criteria, patients had to have been successfully resuscitated from non-traumatic out-of-hospital CPA in our emergency department (ED) and to have undergone brain CT. Successful resuscitation was defined as "the return of spontaneous circulation maintained over 24 hours". All of the patients with successful resuscitation immediately underwent brain CT to determine the cause of CPA according to our protocols. They were then classified into groups with pseudo-SAH [PSAH (+)] and groups without pseudo-SAH [PSAH (-)].

Exclusion criteria included patients who were transferred from another hospital after successful resuscitation, CPA from trauma, futile resuscitation or CPA from subarachnoid haemorrhage. CPA from trauma was excluded because CT differentiation between real SAH and PSAH in trauma cases is difficult.[3,13] CPA from subarachnoid haemorrhage was confirmed by cerebrospinal fluid (CSF) examination or autopsy.

In all enrolled patients, CT scans were performed in the transverse plane parallel to the supraorbitomeatal or orbitomeatal line, with a thickness of 4.5 mm, by using a 16-channel multi-detector CT scanner (Somatom Sensation 16 Channel CT; Siemens, Germany) shortly after successful resuscitation. Non-enhanced CT scans were obtained using parameters of 120 kVp and 320 mAs. Contrast media were not administered to any of the enrolled patients within 24 hours prior to measuring the CT values.

To validate the clinical criteria listed above, CT values [in Hounsfield units (HU)] were compared between the PSAH (+) group and the real SAH (+) group. Some previous studies have reported that the mean CT value (29.0-37.6 HU) in PSAH patients is lower than that in cases of SAH (53.7-70.0 HU).[3,4] In our study, the selected SAH group consisted of 12 patients (35-78 years of age; average, 55.0 years). CT values of HDAs in the Sylvian fissure were measured bilaterally on every side where HDAs first appeared (Figure 1). All patients in the PSAH (+) and SAH(+) groups had bilateral lesions. One radiologist, who was neither involved with nor aware of our study, performed the measurements of CT values in both groups.

PSAH was diagnosed by autopsy, CSF examination and by using the following criteria: (1) high-attenuation areas (HDAs) along the cisterns or cortical sulci on the brain CT; (2) no clumped HDAs in the ventricles or sulci on the brain CT; (3) severe brain swelling on the brain CT; (4) no visible aneurysm on brain CT angiography; (5) no typical presentation of SAH when patients first collapsed, and (6) intracranial HDAs not noted on the first CT but appearing in the cisterns or sulci on the follow-up CT. These clinical criteria were first established by Yazawa in their study on PSAH.[4]

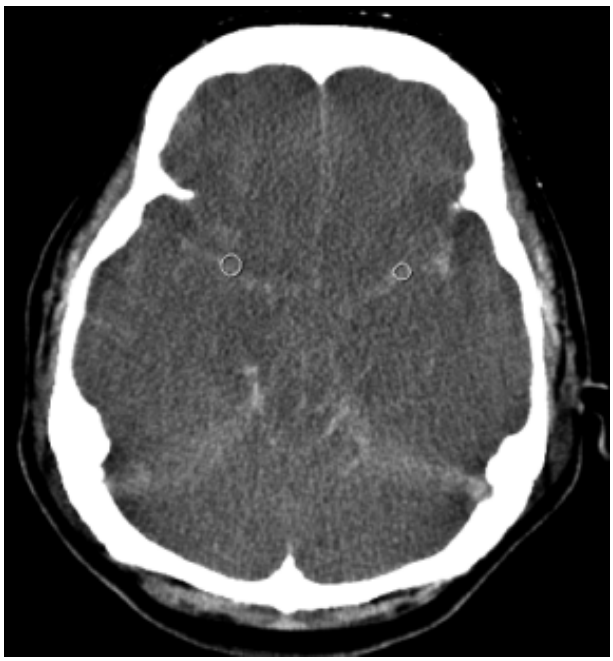


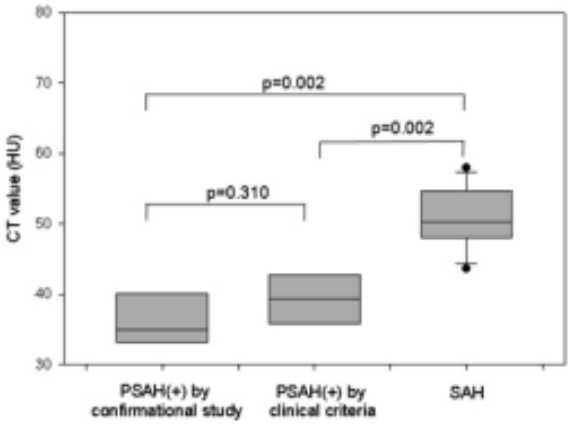
Figure 1. Areas where CT values (HU) were measured. CT values of high-density areas in the Sylvian vallecula/fissure were measured bilaterally on every side where HDAs first appeared.

The PSAH (+) and PSAH (-) groups were compared with respect to a number of demographic, clinical, and physiological variables. All blood chemistry variables were measured at the patient's initial ED visit. Duration of CPA and pre-hospital resuscitation were estimated by the record of paramedics and patient's history. The cause of CPA was assumed based on the patient's history and other clinical findings. The patient's neurological outcome was determined according to her or his Cerebral Performance Category (CPC) score upon discharge.

Continuous data are expressed as the mean ± standard deviation. The data were analysed using the SPSS 12 statistics program (SPSS Inc., USA). Stepwise forward-logistic regression analysis was employed to determine potential risk factors associated with the development of PSAH. Variables with a univariate P value of <0.05 were entered into the model. The dependent variables included gender, age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, arrest time, resuscitation time, cause of arrest, arrest rhythm, systolic and diastolic blood pressure, heart rate, and blood chemistry variables such as glucose, aspartate transaminase (AST), alanine transaminase (ALT), PCO_2, pH, base excess, and lactate. Statistical analysis for univariate variables was performed using the Mann-Whitney test and Fisher's exact test. In evaluating the results of the logistic regression analysis, a p value of <0.05 was considered as significant.

Results

PSAH (+) was recognised in 12 patients (31.6%) out of a total of 38 enrolled patients. CT values were 36.3±3.7 in the PSAH (+) group diagnosed by autopsy or CSF study, 38.2±2.3 in PSAH (+) groups diagnosed by clinical criteria, and 50.5±4.0 in the real SAH (+) group (Figure 2). CT values among the three groups showed statistically significant differences according to the Kruskal-Wallis test (p=0.000). There were no significant differences in CT values between the PSAH (+) group diagnosed by autopsy or CSF study and the PSAH (+) groups diagnosed by clinical criteria, according to the Mann-Whitney test (p=0.310). However, CT values differed significantly between the real SAH (+) group and PSAH (+) groups diagnosed by either of confirmation study and clinical criteria (p=0.002, p=0.002), according to the Mann-Whitney test. CT values in the PSAH (+) groups, whether diagnosed by confirmation study or clinical criteria,

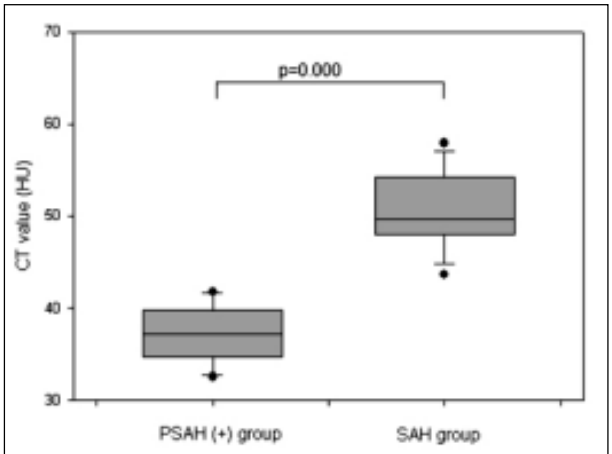


CSF=cerebrospinal fluid; PSAH=pseudo-subarachnoid haemorrhage; SAH=subarachnoid haemorrhage

Figure 2. CT values among three groups: PSAH (+) group with autopsy and CSF examination, PSAH (+) group with clinical criteria, and SAH group.

were 37.3±3.1, and there were statistically significant differences in CT values between PSAH (+) groups and the real SAH (+) group (Mann-Whitney test, p=0.000) (Figure 3).

Table 1 shows the clinical characteristics of the enrolled patients. PSAH was more common in males (p=0.042). The mean age of patients was 39.9±10.3 years in the PSAH (+) group, as compared to 54.4±22.0 years in the PSAH (-) group (p=0.038). And the duration of anoxia (from the patient's collapse to the start of resuscitation) was significantly prolonged in the PSAH (+) group than in the PSAH (-) group (41.5±19.0 minutes vs. 26.9±13.9 minutes, p=0.013). There was no statistically significant difference between the groups in the APACHE II score, duration of resuscitation, or arrest rhythm (p=0.297, 0.185, 0.172, respectively).



CSF=cerebrospinal fluid; PSAH=pseudo-subarachnoid haemorrhage; SAH=subarachnoid haemorrhage

Figure 3. CT values among the two groups: PSAH (+) group with any diagnostic method (autopsy, CSF examination, and clinical criteria) and SAH group.

Table 1. Demographics and clinical characteristics of enrolled patients

		PSAH (+) (n=12)	PSAH (-) (n=26)	p value
Gender (Male:Female)		8:4	8:18	0.042
Age (years)		39.9±10.3	54.4±22.0	0.038
APACHE II score		27.3±6.5	24.7±6.4	0.297
Duration of anoxia (minutes)		41.5±19.0	26.9±13.9	0.013
Duration of resuscitation (minutes)		22.7±10.9	17.4±8.9	0.185
Arrest cause (n)	Respiratory	9	15	0.256
	Nonrespiratory	3	11	
Arrest rhythm (n)	Asystole	9	12	0.172
	PEA	3	10	
	VF	0	4	
CPC score	CPC 1 (n)	0	4	0.037
	CPC 4 (n)	5	17	
	CPC 5 (n)	7	5	
AST (U/L)		343.6±226.7	388.0±633.7	0.393
ALT (U/L)		305.9±290.7	317.9±640.7	0.185
PCO_2 (mmHg)		78.9±56.7	63.6±32.0	0.769
pH		6.88±0.26	7.05±0.23	0.021
Base excess (mmol/L)		-19.0±9.8	-12.4±9.0	0.051
Lactate (mmol/L)		14.8±3.3	9.9±3.7	0.001
Glucose (mg/dl)		313.9±125.9	255.2±88.6	0.076

ALT=alanine transaminase; APACHE=Acute Physiology and Chronic Health Evaluation; AST=aspartate transaminase; CPC=Cerebral Performance Category; PEA=pulseless electrical activity; PSAH=pseudo-subarachnoid haemorrhage; VF=ventricular fibrillation

On the other hand, the incidence of respiratory arrest as a cause of CPA in the PSAH (+) group was significantly higher than that in the PSAH (-) group (p=0.021). Outcomes measured by CPC scores were also significantly different between the two groups (p=0.037).

Arterial pH in the PSAH (+) group was significantly lower than that in the PSAH (-) group (6.88±0.26 vs. 7.05± 0.23; p=0.021). Blood lactate level in the PSAH (+) group was significantly higher than that in the PSAH (-) group (14.8±3.3 mmol/L vs. 9.9±3.7 mmol/L, p=0.001). Other variables were not significantly different between the two groups. Logistic regression analysis of the risk factors for the development of PSAH revealed that blood lactate level and the duration of anoxia were significant risk factor for the development of PSAH (with odds ratios and p values of 1.92; p=0.01 and 1.13; p=0.02, respectively, Table 2).

Discussion

We used several methods to confirm PSAH in our study. The first method was autopsy. In our study, two patients underwent autopsies. Another method was CSF examination. CSF examinations, available for six patients, were performed during the insertion of intracranial pressure monitoring sensors. We used the clinical criteria originally developed by Yuzawa et al in their study on PSAH to rule out SAH in another four patients.[4] These four patients had clear causes of CPA – acute myocardial infarction – and none had a clinical presentation of SAH, such as headaches, vomiting, or decreased consciousness, when they collapsed. In these four patients, PSAH were seen on an initial brain CT in the emergency room and disappeared on a follow-up brain CT three days later.

Table 2. Risk Factors associated with development of PSAH

Variable	Odds ratio	p-value	95% CI
Lactate	1.92	0.01	1.18-3.13
Duration of anoxia	1.13	0.02	1.02-1.26
Male gender	7.08	0.22	0.32-157.11
Arterial pH	0.46	0.80	0.00-191.30
Age	0.94	0.28	0.83-1.06

CI=confidence interval; PSAH=pseudo-subarachnoid haemorrhage

To validate our clinical criteria, CT values were compared between the PSAH (+) group and the real SAH(+) group: CT values for the Sylvian fissure in these four patients were lower than those in the real SAH(+) group significantly. And there were no significant differences in CT values between the PSAH (+) group diagnosed by autopsy or CSF study and the PSAH (+) groups diagnosed by clinical criteria, according to the Mann-Whitney test (p=0.310) (Figures 2 and 3). Further studies are needed to clarify criterion of CT value for Sylvian fissure in PSAH.

In our study, PSAH was found in 12 out of 38 patients (31.6%) who had been successfully resuscitated from cardiac arrest. The incidence of PSAH has not yet been elucidated. Yuzawa et al found that PSAH developed in approximately 20% of patients with post-resuscitation encephalopathy,[4] and potentially representing the first systematically investigated study on the incidence of PSAH. PSAH has been viewed as a rare phenomenon:[2,3] however, our results together with those of Yuzawa et al suggest that PSAH is not rare in patients with post-resuscitation encephalopathy.[4] The mean age of the PSAH (+) group was significantly lower than that of the PSAH (-) group (Table 1). Interestingly, 83.3% of the patients in the PSAH (+) group were under the age of 50, compared to only 34.6% in the PSAH (-) group. These findings might be related to atrophy of the brain parenchyma in old age: brain volume decreases and cerebrospinal fluid volume increases with advancing age;[14,15] therefore, the increase in intracranial pressure secondary to cerebral oedema might be delayed. This delay of increase in intracranial pressure might delay or prevent the development of PSAH.

In our study, all PSAHs were accompanied by cerebral oedema, in accord with other studies.[1-3,7-9] We considered that PSAH might be more common in young patients. Although the exact mechanisms remain unknown, cerebral oedema might be related to PSAH. Subarachnoidal spaces narrow when intracranial

pressure rises due to cerebral oedema. The resultant subarachnoidal space becomes relatively devoid of CSF and is instead filled with a larger fraction of meninges and blood vessels than in the normal state, thus potentially increasing the CT atennuation.[3] This increased attenuation of CT would appear as PSAH on a brain CT. There have been several mechanisms proposed for the development of PSAH: calcification of dural structures or blood vessels, volume averaging, the presence of a purulent substance, displacement of hypodense CSF,[3] and cerebral venous congestion or engorgement.[2] However, the exact mechanisms causing the appearance of PSAH remain largely unclear.

PSAH was considered as a poor prognostic factor in several previous reports.[4,8-12] In our study, the PSAH (+) group also experienced more grave neurological outcomes (Table 1). Blood lactate levels in the PSAH (+) group were significantly higher than those in the PSAH (-) group (14.8±3.3 mmol/L vs. 9.9±3.7 mmol/L, p=0.001). Lactate in the blood is one of the causes of increased anion-gap metabolic acidosis and can be elevated when tissue oxygenation is impaired or anaerobic metabolism is increased, such as during CPA. The rise in lactate levels in victims of CPA is the consequence of decreased oxygen delivery secondary to CPA, which leads to an altered redox state, thereby favoring conversion of pyruvate to lactate.[16,17] Furthermore, the duration of anoxia was more prolonged in the PSAH (+) group than in the PSAH (-) group (41.5±19.0 minutes vs. 26.9±13.9 minutes, p=0.013). Blood lactate level and duration of anoxia were found to be significant risk factors for the development of PSAH in our logistic regression analysis (with odds ratios and p values of 1.918, p=0.009 and 1.132, p=0.023, respectively).

These findings suggest that patients with PSAH suffered more severe anoxic insults - high lactate level and longer duration of anoxia - and that these anoxic insults, in turn, might affect the development of PSAH. The relationship between anoxic insult and PSAH could be explained as follows: anoxic insult could cause vasogenic cerebral oedema in which the blood-brain barrier is broken down, and as mentioned above, this vasogenic cerebral oedema may then trigger the development of PSAH.

In our opinion, the causes of the poor prognoses in the PSAH (+) group might be the consequence of severe anoxic insult, not by PSAH itself. Although PSAH was known as poor prognostic factor in post-resuscitation period, PSAH itself was just a phenomenon that could be seen in post-resuscitation encephalopathy, and fundamentally severe anoxic insult played an important role in neurological outcomes in the PSAH (+) group.

Our study has some limitations. Because PSAH was known as rare phenomenon, this study was conducted retrospectively, so we could not control the bias. Second, although meaningful statistical analysis could be performed, the number of patients with PSAH were too small and we could not make a strong conclusion. Further large and prospective studies are needed. Third, although we tried to rule out true SAH through the use of several methods, four patients with PSAH still remained unconfirmed with respect to PSAH.

Conclusions

High lactate level and longer duration of anoxia are risk factors for the development of PSAH in patients who are successfully resuscitated from out-of-hospital CPA. These results suggest that PSAH itself can be a phenomenon seen in post-resuscitation encephalopathy and the causes of poor prognoses in the PSAH (+) group may be the consequence of high lactate level and longer duration of anoxia.

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