

Comparison of cerebral-cardiac syndrome caused by nonaneurysmal or aneurysmal subarachnoid hemorrhage

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Abstract. – OBJECTIVE: To investigate the difference between myocardial injuries caused by nonaneurysmal subarachnoid hemorrhage (SAH) or aneurysmal SAH.

PATIENTS AND METHODS: A total of 92 in-patients with SAH at early stage (within 48h), who were treated in our hospital from 2008 to 2014 were enrolled in this study. Differences in cerebral-cardiac syndrome seen in perimesencephalic subarachnoid hemorrhage (PMSAH), non-perimesencephalic subarachnoid hemorrhage (n-PMSAH), and aneurysmal subarachnoid hemorrhage (aSAH) were recorded based Hunt-Hess scores, electrocardiogram/echocardiography findings, and serum myocardial enzymes.

RESULTS: The Hunt-Hess grade was relatively lower in the PMSAH group (mainly at grades I and II) than in aSAH group and n-PMSAH group. The ECG score was significantly lower in the PMSAH Group than in the aSAH or n-PMSAH Group. In the PMSAH group, the left ventricular function was normal; in contrast, the left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular wall thickness, and left ventricular ejection fraction showed certain abnormalities in the aSAH group and n-PMSAH group. The myocardial enzymes remarkably increased only in the aSAH group.

CONCLUSIONS: In PMSAH patients, the lower Hunt-Hess grade, milder ECG abnormalities, less changes in cardiac enzymes and echocardiography are associated with better prognosis. The clinical course and myocardial injuries are poorer in n-PMSAH patients when compared with the PMSAH patients but better than aSAH patients.

Key words:

Perimesencephalic subarachnoid hemorrhage, Subarachnoid hemorrhage, Cerebral-cardiac syndrome, PMSAH, n-PMSAH.

Introduction

Subarachnoid hemorrhage (SAH) is a common acute cerebrovascular disease, with aneurysms and cerebral vascular malformation as the main etiology. However, no hemorrhagic evidences of etiology for such aneurysms were found in approximately 5%-28% patients undergoing whole cerebral angiography in clinical practice. Perimesencephalic regions were involved in certain proportion of these SAH patients (1/3-2/3) with negative whole cerebral angiography findings. For these patients, there were unique clinical manifestations, treatment and prognosis. Currently, this disease type is defined as perimesencephalic subarachnoid hemorrhage (PMSAH)¹, which is also known as benign subarachnoid hemorrhage. Since nonaneurysmal subarachnoid hemorrhage was not restricted to the perimesencephalic region for a considerable number of patients, this disease species is defined as non-perimesencephalic subarachnoid hemorrhage (n-PMSAH)². Since Dozzi tried to explore the relationship between cardiac dysfunction and cerebrovascular disease in 1937³, the importance of cerebrovascular disease in the development of myocardial injury, cardiac arrhythmia and acute myocardial infarction has been confirmed by many researchers⁴. Moreover, some patients died of such fatal arrhythmias and cardiac arrest. In clinical practice, this secondary heart damage induced by acute cerebrovascular disease is referred as cerebral-cardiac syndrome (CCS). In the present study, enrolled patients were divided into PMSAH, n-PMSAH and aneurysmal subarachnoid hemorrhage (aSAH) groups. Hunt-Hess rating scale was employed to assess the extent of nerve damage. Changes of ECG, myocardial enzymes and cardiac ultrasound findings were examined to compare the variance of cerebral-cardiac syndrome among these groups.

Patients and Methods

Clinical Data

Inclusion Criteria

According to the diagnostic criteria of subarachnoid hemorrhage formulated by the 4th National Conference on Cerebrovascular Disease, 86 patients who were admitted to the Department of Neurology of our hospital due to subarachnoid hemorrhage from February 2008 to February 2014 were included. Inclusion criteria were: no family history of subarachnoid hemorrhage, not receiving anti-platelet regimen, incident subarachnoid hemorrhage, and disease onset within 48 hours. All patients underwent emergency cranial CT examinations before or at admission and were diagnosed to be SAH. The existence of any aneurysms was confirmed by computed tomography angiography (CTA) or digital selective angiography (DSA) within one week. 26 Males and 34 females, aging from 42 to 78 years, were included, with the mean age of 56.4 years. According to the PMSA diagnostic criteria, enrolled patients were divided into three groups: PMSAH Group (26 patients), n-PMSAH Group (28 patients) and aSAH Group (32 patients).

Exclusion criteria:

(1) Subarachnoid hemorrhage induced by other etiologies, such as trauma, intracranial hemorrhage, arteriovenous malformation, and aneurysm;

(2) documented heart disease before admission, such as coronary heart disease, valvular heart disease, arrhythmias, etc.; (3) ECG abnormalities within three months prior to admission; and (4) hypertensive heart disease for patients with hypertension.

Diagnostic criteria for PMSA

According to the diagnostic criteria proposed by Rinkel et al⁵: (1) patients underwent cranial CT examination within 48 hours, with the hemorrhagic center located in the frontier of perimesencephalic region, downward extension to anterior myelencephalon, and forward to posterior longitudinal fissure without fully occupied, outward to the internal horizontal portion of lateral fissure without external portion involved, excluding little hemorrhage; (2) a small amount of depositing intraventricular hemorrhage; and (3) no parenchymal hemorrhage (Figure 1).

Diagnostic criteria for n-PMSAH

According to the diagnostic criteria proposed by Gupta et al⁶: the majority of hemorrhage was located at the intersection pool, exterior cistern and interhemispheric pool, with some perimesencephalic regions involved. However, majority of the hemorrhage was located at other brain pools (Figure 2).



Figure 1. A cranial CT image of patients with nonaneurysmal subarachnoid hemorrhage.

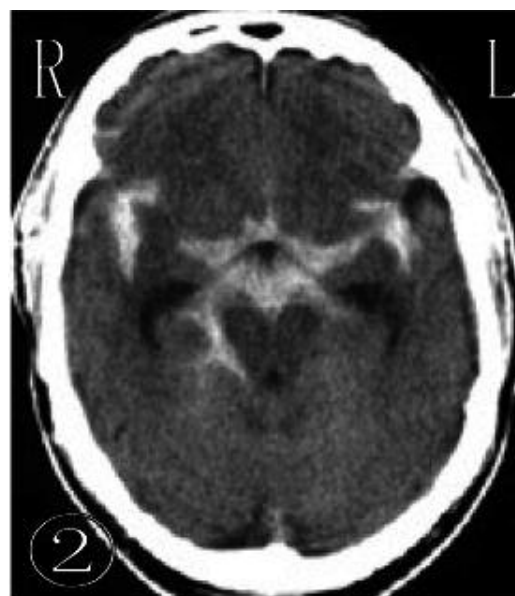


Figure 2. A cranial CT image of patients with perimesencephalic subarachnoid hemorrhage.

Methods

The basic information of patients was documented at admission to evaluate the extent of disease condition (Hunt-Hess Scale). After admission, bedside 12-lead ECG was performed within 24 hours and abnormalities were defined as follows: (1) Sinus tachycardia, heart rate >100 bpm, absence of rhythm disorders; (2) Sinus bradycardia, heart rate < 60 bp, no rhythm disorder; (3) QT prolongation ($\geq 0.44s$); (4) ST segment changes: ST-segment elevation (≥ 0.1 mv), ST segment depression (≥ 0.05 mv). Assessment was based on Kawasaki et al scale criteria⁷, and scores represented the respective frequencies of pathologic Q waves, ST segment elevation or depression, and T wave prolongation. Any of above performance was counted as one point.

In the next morning of admission, venous blood samples were collected and submitted to our laboratory. Biomarkers for cardiac injury, such as troponin I (TnI), and creatine kinase and its isozymes (CK-MB), were quantitatively assayed by using enzyme-linked immune-sorbent assays (ELISA). For abnormalities of the first test, repeated tests were performed on day-3 and day-7.

After admission, echocardiography examinations were performed within 48 hours. Variables to determine include left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular wall thickness (LVPWH), left ventricular ejection fraction (LVEF) and ventricular wall motion.

Statistical Analysis

Statistical analyses were performed on the platform of SPSS 16.0 software (SPSS Inc., Chicago, IL, USA), with results represented as mean \pm SD. Pairwise mean comparison was analyzed between the two groups by *t*-test; and multiple mean comparisons were analyzed were ana-

lyzed by one-way ANOVA, and a *p* < 0.05 denotes the statistical significance of difference.

Results

Stratified Hunt-Hess comparisons among PMSAH, n-PMSAH and aSAH groups

The severity of condition was judged based on the Hunt-Hess scale. As shown by the results, less severity was observed in condition for patients with PMSAH, with Grade-I or -II for the majority of patients; and more severity was observed in patients with aSAH, including 22 patients with Grade III-V. The condition of severity of patients with n-PMSAH was between the above two groups, as shown in Table I.

Comparisons of ECG results among PMSAH, n-PMSAH and aSAH Groups

Based on the findings of ECG monitoring changes, there were ECG abnormalities in all three groups, but the frequency of abnormality was higher in the PMSAH Group than in the aSAH or n-PMSAH Group (Table II). Moreover, the ECG score was significantly lower in the PMSAH Group than in the aSAH or n-PMSAH Group (1.6 ± 0.8 vs 5.8 ± 3.1 ; 4.3 ± 1.1 , *p* < 0.01). These differences were statistically significant. There was no significant difference in ECG scores between aSAH and n-PMSAH Groups.

Comparisons of cardiac ultrasound results among PMSAH, n-PMSAH and aSAH Groups

All enrolled patients underwent cardiac ultrasound examinations. As shown by the results, normal findings of left ventricular function were observed in patients of the PMSAH Group, without reporting inner diameter expansion of heart cavity and wall motion abnormalities. There were abnormalities of LVESD, LVEDD, LVPWH

Table I. Comparisons of HUNT-HESS scores among the three groups (frequency, %).

Group	Number	HUNT-HESS Grade			
		Grade I	Grade II	Grade III	Grade IV/V
Group aSAH	32	3 (9.3)	7 (21.9)	14 (43.8)	8 (25.0)
Group n-PMSAH	28	4 (14.3)	19 (67.9)	2 (7.1)	3 (10.7)
Group PMSAH	26	3 (11.5)	22 (84.6)	1 (3.8)	0 (0)

Table II. Comparisons of ECG abnormality scores among three groups (\pm s).

Group	N	Number of ECG abnormalities (percentage)				ECG Scores
		Elevation of ST segment	Depression of ST segment	QT prolongation	Q wave abnormalities	
Group aSAH	32	9 (28.13%)	13 (40.63%)	6 (18.75%)	2 (6.25%)	5.8 \pm 3.1
Group n-PMSAH	28	7 (25.00%)	15 (53.57%)	4 (14.29%)	0 (0)	4.3 \pm 1.1
Group PMSAH	26	3 (11.54%)	12 (46.15%)	2 (7.69%)	0 (0)	1.6 \pm 0.8*

Note: Compared with that of aSAH Group, * $p < 0.05$.

and LVEF to various extents in aSAH and n-PMSAH Groups. There were 9 and 4 cases of abnormal wall motion, respectively. See Table III for details.

Comparison of troponin levels among the three groups of PMSAH, n-PMSAH and aSAH

In the next morning of admission, venous blood samples were collected and submitted to our laboratory for myocardial enzyme tests (Table IV). As shown by the results, the highest levels of TnI, CK and CK-MB of myocardial enzyme panel were observed for aSAH patients. Only 7 cases of myocardial enzyme elevations were observed in 26 PMSAH patients. The differences were statistically significant ($p < 0.01$).

Discussion

Van Gijin et al⁸ first proposed the concept of PMSAH in 1985 based on the findings of imaging examinations. In their reports, for patients with the hemorrhage site located at the perimesencephalic region, the clinical symptoms were relatively less severe, and mild-to-moderate distending pain was identified to be the main manifestations of headache, with temporal or occipital regions most commonly affected. The conditions were fully recovered after three months of onset. No relapse was observed over the 18 months of follow-up.

Therefore, for the first time, these authors considered the perimesencephalic SAH with no aneurysms or other abnormalities in angiography, mild symptoms and favorable prognosis to be PMSAH. In this study, three groups of patients were evaluated based on Hunt-Hess scales. The least severity in neurological deficit was observed in PMSAH patients, with Grade I/II for the majority.

Perimesencephalic regions include basal cistern, cerebral peduncle, ambient cistern and quadrigeminal cistern. As a unique subtype of subarachnoid hemorrhage, the cause of PMSAH has not yet been fully understood. Possible etiologies include expansion and bleeding of veins or capillaries, rupture of perforating artery, occult arteriovenous malformation, secondary bleeding induced by occlusion of small perforating branches. The center of bleeding was concentrated around perimesencephalic regions⁹. If there were diffuse bleeding or blood clots in the merger longitudinal or lateral cistern, non-PNSH origin of bleeding should be considered. Although the clinical manifestations of such nervous system damage were relatively less severe, patients might experience other complications such as hyponatremia or heart abnormalities¹⁰. Imaging changes and neurological injury have been highlighted in prior PMSA related studies, and there were few investigations on the classification of myocardial injury following PMSAH, n-PMSAH and aSAH. Therefore, the post-SAH cerebral-cardiac syndrome has been investigated in this study.

Table III. Comparisons of cardiac ultrasound results among PMSAH, n-PMSAH and aSAH Groups (\pm s).

Group	N	LVESD	LVEDD	LVPWH	LVEF	Abnormal wall motion (N)
Group aSAH	32	47.23 \pm 2.01	49.76 \pm 3.69	9.28 \pm 0.76	42.17 \pm 2.48	9
Group n-PMSAH	28	48.18 \pm 1.86	50.23 \pm 2.82	9.86 \pm 0.49	43.15 \pm 1.59	4
Group PMSAH	26	38.23 \pm 2.31*	40.19 \pm 3.08*	8.99 \pm 0.92*	53.23 \pm 1.24*	0

Note: Compared with that of aSAH Group, * $p < 0.05$.

Comparison of cerebral-cardiac syndrome

Table IV. Comparisons of myocardial enzyme panel among these three groups (\pm s).

Group	N	TnI (ng/ml)	CK (U/L)	CK-MB (U/L)
Group aSAH	32	4.18 \pm 1.20	389.12 \pm 60.41	35.26 \pm 12.30
Group n-PMSAH	28	3.06 \pm 0.83	293.56 \pm 50.39	26.14 \pm 10.52
Group PMSAH	26	1.06 \pm 0.26*	198.67 \pm 45.23*	19.68 \pm 8.93*

Note: Compared with that of aSAH Group, * $p < 0.05$.

The cardiac injury post subarachnoid hemorrhage belongs to the scope of brain-heart syndrome, with ischemia changes such as ST segment elevation of depression, flat T-wave or inversion, Q-T prolongation as shown by ECG examinations within one week of SAH onset, ventricular contraction, sinus tachycardia, bradycardia or atrioventricular block arrhythmias and other changes persisting for several days or weeks as the main manifestations. Its nature of functional or organic changes remained controversial. Based on above changes, ECG score has been recently employed to determine the post-SAH ECG abnormalities. Kawasaki et al⁷ described ECG score was an independent factor of SAH patient mortality. In this study, ECG abnormalities were analyzed by ECG scores within 24 hours of admission, suggesting the presence of ECG abnormalities to variable extent in patients of three groups. However, the incidence of ECG abnormality was lowest in PMSAH patients, with an overt lower ECG score compared with those of other two groups. ECG injury appeared to be less severe in patients with mild neurological damage (Hunt-Hess grade). Aneurysm rupture induced hemorrhage mainly affected cerebral arterial circle (Willis circle). The result of direct stimulation to the cardiovascular center, such as the hypothalamus and brain stem and Willis circle induced certain region changes of cardiac autonomy was consistent to the pathological mechanism of ECG abnormalities.

Intra-cardiac structures, heart beat and blood flow could be dynamically demonstrated by echocardiography, which could be useful to detect changes of cardiac function of early stages and to formulate early interventions. Sugimoto et al¹¹ conducted 2D-dimensional echocardiography in 47 SAH patients without prior heart diseases to determine cardiac functions. As shown by the results of this study, for SAH patients with regional wall motion abnormality (RWMA), higher Hunt-Hess classification, and CK and CK-MB levels, as well as higher initial heart rate were observed,

concomitant with a high incidence of inverted T waves. In that study, a detailed classification comparison was conducted for SAH patients. As shown by echocardiography among PMSAH, n-PMSAH and aSAH patients, the variables of PMSAH patients were essentially in the normal range, without the observation of regional wall motion abnormality, and left ventricular expansion to variable extents and decrease of ejection fraction were observed in n-PMSAH and aSAH patients, with regional wall motion abnormalities reported in 4 and 9 cases respectively. However, no follow-up re-examinations were implemented for patients with echocardiography abnormalities in this study.

SAH patients often experienced concomitant elevation of myocardial enzymes in the early stages of disease onset, suggestive of the presence of secondary myocardial damage. This injury was generally considered to be reversible and could be gradually recovered in response to the treatment of primary disease. As described by Der Bilt et al¹², TnI elevation was associated with increased risk of cardiopulmonary complications, delayed encephalopathy and death. However, there were relatively few studies dealing with myocardial injury induced by non-aneurysmal or aneurysmal subarachnoid hemorrhage. The levels of CK, CK-MB and TnI were examined in this study, in which TnI level was one of specific indices for myocardial injury. As shown by the results, elevations of cardiac enzyme panel to variable extents were observed in patients of the three groups. The incidence of perimesencephalic subarachnoid hemorrhage and the elevations of cardiac enzyme panel were relatively low in extent. The severity of myocardial injury for n-PMSAH patients was between that of PMSAH patients and of aSAH patients.

Conclusions

Based on the four data sets of comparative analyses, lower Hunt-Hess grades were associated with less changes of ECG findings, cardiac

enzymes and echocardiography, as well as more favorable prognosis, for patients with PMSAH. The clinical course and severity of myocardial injury for patients with n-PNSAH were inferior to those of patients with PMSAH. However, these variables were more favorable than those of patients with aneurysmal subarachnoid hemorrhage. Therefore, the severity of SAH was proposed to be positively proportional to cardiac performance. Thus, changes of ECG and cardiac enzyme panels should be actively monitored after SAH attack. Early detection and intervention were generally recommended.

Conflict of interest

The Authors declare that they have no conflict of interests.

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