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Subarachnoid Hemorrhage Complicated With Neurogenic Pulmonary Edema and Takotsubo-Like Cardiomyopathy

Joji INAMASU,[1,2] Masashi NAKATSUKASA,[2] Keita MAYANAGI,[2]
Satoru MIYATAKE,[3] Keiko SUGIMOTO,[4] Takuro HAYASHI,[1]
Yoko KATO,[1] and Yuichi HIROSE[1]

Departments of [1]Neurosurgery and [4]Laboratory Medicine,
Fujita Health University School of Medicine, Toyoake, Aichi; Departments of
[2]Neurosurgery and [3]Emergency Medicine, Saiseikai Utsunomiya Hospital, Utsunomiya, Tochigi

Abstract

Patients with poor-grade subarachnoid hemorrhage (SAH) are often complicated with acute cardiopulmonary dysfunctions, particularly neurogenic pulmonary edema (NPE) and takotsubo-like cardiomyopathy (TCM). This study retrospectively investigated the incidence, demographics, clinical characteristics, and outcomes of patients with SAH complicated with both NPE and TCM (NPE-TCM). The effects of aneurysm location and other clinical variables on the incidence of NPE-TCM were also investigated. Among 234 SAH patients treated during 5-year period, 16 (7%) presented with NPE, and transthoracic ultrasonography revealed that 14 of these 16 patients (88%) also had TCM. All 14 patients with NPE-TCM had poor-grade SAH (World Federation of Neurosurgical Societies grades IV and V). Ruptured posterior circulation aneurysm was predictive of NPE-TCM, but other clinical variables were not. Eight of the 14 patients with NPE-TCM could undergo treatment for ruptured aneurysm. Long-term outcomes were favorable in 5 of the 8 patients. Grade IV SAH patients had significantly better outcomes than grade V patients. TCM develops frequently in SAH patients presenting with NPE, and transthoracic ultrasonography should be conducted routinely in that population. Patients with ruptured posterior circulation aneurysm may have elevated risk of developing NPE-TCM. Endovascular obliteration of the aneurysm may be preferable to open surgery, but the optimal treatment modality needs to be evaluated further. Considering the limited number of SAH patients complicated with NPE-TCM, a multi-center cooperative study may be required.

Key words: aneurysm, neurogenic pulmonary edema, posterior circulation, takotsubo-like cardiomyopathy, subarachnoid hemorrhage

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is often complicated with acute cardiopulmonary dysfunctions, particularly neurogenic pulmonary edema (NPE) and takotsubo-like cardiomyopathy (TCM).[3,9,19,25] The association of NPE with poor-grade SAH has been known for years.[9,25,29,34,35] The reported incidence of NPE in SAH patients ranges from 2% to 29%.[9,25] TCM, also known as stunned myocardium,[19] has been associated etiologically with SAH.[3,18,19,27] The reported incidence of TCM in SAH patients ranges from 4% to 15%.[3,19] Unlike NPE, TCM seems to occur in patients with good-grade SAH as well.[19] The nomenclature of *takotsubo-like* cardiomyopathy[2,32] is important to differentiate from idiopathic takotsubo cardiomyopathy, which by definition should not have an extra-cardiac cause.[16] Although these two complications had been regarded as separate entities in the past,[18,35] recent studies indicate that they share a common pathophysiology and may coexist in the same patient.[12,20,21,24,31] The common pathophysiology involves massive catecholamine release, particularly norepinephrine, into the circulation immediately after aneurysm rupture, and is responsible for endothelial damage, vasoconstriction, and increased vascular permeability.[7,20,21] However, how often SAH patients complicated with NPE also have concomitant TCM (NPE-TCM) remains unclear, since evaluation of cardiac wall motion using transthorac-

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ic ultrasonography is rarely conducted in this population. Ruptured posterior circulation aneurysms may also cause NPE more frequently compared with anterior circulation aneurysms.[25,26] In our institution, transthoracic ultrasonography is performed routinely in the emergency department for SAH patients presenting with the clinical/radiographic signs of NPE, allowing investigation of the incidence and demographics of SAH patients complicated with NPE-TCM.

The present study investigated the clinical characteristics and outcomes of SAH patients complicated with NPE-TCM, to identify the effects on the incidence of NPE-TCM of aneurysm location and other clinical variables.

Patients and Methods

I. Patient population

A total of 234 patients with spontaneous SAH were admitted to our institution between January 2005 and December 2009. Brain computed tomography (CT) and portable chest radiography were performed for all patients suspected of SAH immediately after arrival at the emergency department. If brain CT detected SAH, three-dimensional CT angiography was performed to search for a ruptured aneurysm. Clinical criteria for NPE included the auscultation of crackles that suggested fluid in the lungs and presence of frothy pink tracheal fluid.[25] Radiographic criteria for NPE included sharp definition of pulmonary markings accompanied by blurring or haziness of the perivascular outlines and loss of demarcation of hilar shadows.[25] The radiographs were interpreted by board-certified specialists in emergency medicine, and patients who fulfilled both clinical and radiographic criteria were determined to have NPE. Transthoracic ultrasonography was performed extensively by the same physicians. Echographic criteria for TCM included the presence of severe regional wall motion abnormalities preferentially affecting the apical and midventricular segments.[19] Electrocardiography (ECG) was also performed in the emergency department and interpreted by the same physicians. Abnormal ECG findings included presence of ST segment elevation/depression, QT interval (QTc) prolongation, and inversion of T-wave. SAH patients complicated with NPE-TCM were identified from an institutional database, and demographic data, clinical characteristics, and outcomes were retrospectively evaluated. The incidence of NPE-TCM was calculated, and clinical variables predictive of NPE-TCM were evaluated with logistic regression analysis.

II. Clinical management

The treatment of choice for SAH patients complicated with NPE-TCM in our institution was endovascular obliteration of the ruptured aneurysm in the acute stage. However, clipping of the aneurysm in the acute stage was performed if the shape or size of the aneurysm was considered unfit for coiling or if no endovascular neurosurgeon was available, and the final treatment decision was made by the on-call neurosurgeon. Postoperative management included placement of a spinal catheter to evacuate the subarachnoid clot, and administration of intravenous fasudil hydrochloride (Mitsubishi-Tanabe Pharma, Osaka), low molecular weight dextran, and albumin to attenuate vasospasm. The treatment goal during the immediate postoperative period was to maintain *normovolemia* instead of *hypervolemia* to avoid exacerbation of NPE-TCM. Central venous catheters were placed and central venous pressure was monitored routinely. In contrast, pulmonary artery catheters were placed only rarely. As intravenous vasopressors, dopamine was used primarily. The use of norepinephrine and dobutamine was avoided as far as possible because of the risk of exacerbating NPE-TCM.[20,28] Only the aneurysm that had ruptured was considered in the analysis of patients with multiple aneurysms. Patients with perimesencephalic SAH and patients presenting with cardiac arrest were excluded.

III. Statistical analyses

Statistical analyses were performed with StatView 4.5 (Abacus Concepts, Piscataway, New Jersey, USA). In addition, SPSS for Windows ver. 10.0 (SPSS Inc., Chicago, Illinois, USA) was used for logistic regression analysis. Categorical data were compared using the chi-square/Fisher exact test. Values were presented either as mean ± standard deviation or median. $P < 0.05$ was considered statistically significant.

Results

I. Demographics

The 234 patients were aged from 13 to 94 years (mean 63.0 ± 13.3 years). Male:female ratio was 1:1.4. SAH grade on admission, evaluated with the World Federation of Neurosurgical Societies (WFNS) scale,[8] was grade I in 10, grade II in 61, grade III in 35, grade IV in 52, and grade V in 76 patients. CT angiography was performed in 222 patients (95%), but could not be performed in 12 patients, all with grade V SAH, because of poor systemic condition. The ruptured cerebral aneurysm in the 222 patients was located on the anterior com-

municating artery/distal anterior cerebral artery (AComA/dACA) in 67, internal carotid artery (ICA) in 61, middle cerebral artery (MCA) in 58, vertebral artery (VA) in 11, basilar artery (BA) in 9, posterior cerebral artery in 2, and no aneurysms in 14 patients.

II. NPE-TCM and SAH grade

Sixteen of the 234 SAH patients (7%) presented with clinical/radiographic signs of NPE, and transthoracic ultrasonography demonstrated TCM in 14 of these 16 patients (88%). No patients with WFNS grade I–III SAH developed NPE, and transthoracic ultrasonography was not performed in that population. In other words, NPE-TCM occurred exclusively in patients with WFNS grade IV or V SAH. Demographic and ECG findings of the 14 patients are summarized in Table 1. The CT distribution of SAH evaluated with the Fisher classification was grade III in 2 and grade IV in the other 12 patients. Six of the 52 patients with WFNS grade IV SAH (12%) sustained NPE, and 5 (10%) had TCM as well. Meanwhile, 10 of the 76 patients with WFNS grade V SAH (13%) sustained NPE, and 9 (12%) had TCM as well. There was no significant difference in the incidence of NPE-TCM between patients with WFNS grade IV and V SAH ($p = 0.69$). The analysis of ECG abnormality found ST segment elevation/depression in all 14 patients (100%), QTc prolongation in 10 (71%), and T-wave inversion in 3 (21%) (Table 1).

III. Aneurysm location and NPE-TCM in patients with poor-grade SAH

Association between aneurysm location and incidence of NPE-TCM was evaluated in the 116 patients with WFNS grade IV and V SAH who underwent CT angiography. The ruptured aneurysm in the 116 patients was located on the AComA/dACA in 38, the ICA in 30, the MCA in 30, the VA in 9, and the BA in 7 (Fig. 1A). No aneurysm was identified in 2 patients. The ruptured aneurysm in the 14 patients complicated with NPE-TCM was located on the AComA/dACA in 2, the ICA in 4, the MCA in 2, the VA in 4, and the BA in 2 (Fig. 1A). The AComA/dACA, ICA, and MCA aneurysms were combined to form the anterior circulation group ($n = 98$), and the VA and BA aneurysms were combined to form the posterior circulation group ($n = 16$). The incidence of NPE-TCM was significantly higher in the posterior circulation group (8% vs. 38%, $p = 0.004$) (Fig. 1B).

IV. Logistic regression analysis

To identify clinical variables predictive of NPE-TCM, logistic regression analysis was conducted for the 116 patients with WFNS grade IV and V SAH. Clinical variables evaluated were: age, sex, WFNS grade V SAH, and posterior circulation aneurysm. The frequency of each variable is shown in Table 2. The analysis revealed that posterior circulation aneurysm was significantly more predictive of NPE-

Table 1 Demographic and electrocardiographic (ECG) data of 14 patients with subarachnoid hemorrhage complicated with neurogenic pulmonary edema and takotsubo-like cardiomyopathy

Case No.	Age (yrs)/ Sex	WFNS grade	Fisher grade	Aneurysm location	ECG abnormalities		
					ST segment change	QTc prolongation	T-wave inversion
1	62/F	IV	III	lt MCA	+	+	+
2	70/F	IV	IV	rt ICA	+	+	−
3	59/M	IV	IV	AComA	+	+	−
4	58/F	IV	III	rt MCA	+	+	+
5	45/F	IV	IV	rt VA dissection	+	+	−
6	44/F	V	IV	lt VA dissection	+	−	−
7	59/F	V	IV	AComA	+	+	−
8	52/M	V	IV	rt ICA	+	−	−
9	54/M	V	IV	lt ICA	+	+	+
10	76/M	V	IV	BA	+	−	−
11	62/M	V	IV	rt ICA	+	−	−
12	75/F	V	IV	lt VA-PICA	+	+	−
13	64/F	V	IV	BA	+	+	−
14	79/F	V	IV	lt VA-PICA	+	+	−

AComA: anterior communicating artery, BA: basilar artery, F: female, ICA: internal carotid artery, M: male, MCA: middle cerebral artery, QTc: QT interval, VA-PICA: vertebral artery-posterior inferior cerebellar artery, WFNS: World Federation of Neurosurgical Societies.

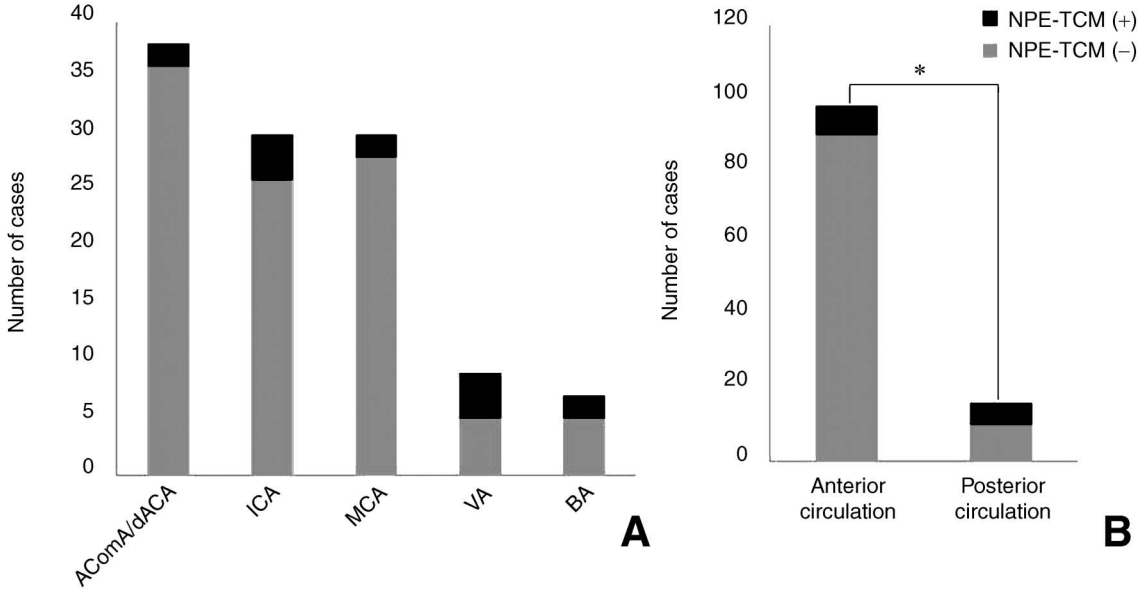

Fig. 1 A: Frequency of neurogenic pulmonary edema (NPE)-takotsubo-like cardiomyopathy (TCM) in poor-grade subarachnoid hemorrhage patients differentiated by aneurysm location. AComA/dACA: anterior communicating artery/distal anterior cerebral artery, BA: basilar artery, ICA: internal carotid artery, MCA: middle cerebral artery, VA: vertebral artery. B: Frequency of NPE-TCM was significantly higher in posterior circulation aneurysms compared to anterior circulation aneurysms (*p = 0.004).

Table 2 Logistic regression analysis evaluating associations between clinical variables and neurogenic pulmonary edema-takotsubo-like cardiomyopathy in the 116 patients with poor grade subarachnoid hemorrhage (SAH)

Variable	Odds ratio	95% Confidence interval	p Value
Age (mean 63.8 ± 16.2 yrs)	1.01	0.97–1.06	0.50
Female sex (60%)	2.48	0.64–9.66	0.19
WFNS grade V SAH (59%)	1.19	0.33–4.31	0.79
Posterior circulation aneurysm (11%)	5.33	1.37–20.32	0.02*

*Statistically significant. WFNS: World Federation of Neurosurgical Societies.

TCM (odds ratio 5.33, 95% confidence interval 1.37–20.72) (Table 2). None of the other clinical variables were significantly more predictive of NPE-TCM.

V. Clinical characteristics and outcomes of patients complicated with NPE-TCM

The clinical characteristics and outcomes of the 14 SAH patients with NPE-TCM are summarized in Table 3. Outcomes at discharge were assessed with the Glasgow Outcome Scale (GOS), and GOS 4–5 was regarded as favorable outcome. All 14 patients required endotracheal intubation, ventilation support, and the administration of intravenous vasopressors during initial resuscitation in the emergency department. All 5 patients with WFNS grade IV SAH underwent treatment for ruptured aneurysm in the acute stage. Clipping was performed in 2 and coiling was performed in 3 patients. The outcomes were GOS 5 in 2, GOS 4 in 2, and GOS 1 in 1 patient. In contrast, neither clipping nor coiling of the aneurysm was feasible because of poor systemic condition in 6 of the 9 patients with grade V SAH. None of these 6 patients achieved long-term survival. The other 3 patients with grade V SAH were treated endovascularly. One patient survived with GOS 4, whereas the other 2 patients died shortly after the procedures. The outcomes were significantly better for grade IV patients ($p = 0.02$). Overall, 5 of the 14 patients with NPE-TCM survived to discharge. Among the 5 survivors, radiographic clearance of NPE had occurred by 3 to 6 days (median 4 days) after SAH onset. Among the 9 patients who died, survival period ranged from 2 to 24 days (median 3 days), and 7 died of primary brain damage. One patient died of vasospasm, and the other patient died of rebleeding of the partially embolized aneurysm (Table 3).

Discussion

This study demonstrated that SAH patients compli-

Table 3 Clinical characteristics and outcomes of 14 patients with subarachnoid hemorrhage complicated with neurogenic pulmonary edema (NPE)-takotsubo-like cardiomyopathy

Case No.	Treatment	Outcome (GOS)	Radiographic clearance of NPE (day after onset)*	Survival period (day); cause of death**
1	clipping	5	3	N/A
2	coiling	4	6	N/A
3	coiling	5	4	N/A
4	clipping	4	4	N/A
5	coiling	1	5	24; rebleeding
6	coiling	4	4	N/A
7	coiling	1	5	8; vasospasm
8	coiling	1	N/A	7; primary drain damage
9	conservative	1	N/A	2; primary drain damage
10	conservative	1	N/A	3; primary drain damage
11	conservative	1	N/A	3; primary drain damage
12	conservative	1	N/A	3; primary drain damage
13	conservative	1	N/A	6; primary drain damage
14	conservative	1	N/A	2; primary drain damage

*Only for those surviving >7 days. **Only for non-survivors. GOS: Glasgow Outcome Scale, N/A: not applicable.

cated with NPE are highly likely to sustain concomitant TCM. In contrast, SAH patients complicated with TCM may not always sustain NPE.[12] The incidence of pulmonary edema in patients with TCM unrelated to SAH is low (22%),[33] suggesting that NPE may not necessarily be a consequence of TCM.

NPE seems to be causally related to the presence of a lesion in and around the medulla oblongata. Both experimental and clinical studies show that destruction or mechanical compression of the dorsal and solitary tract nuclei, which suppress sympathetic activity, leads to acute change in pulmonary vascular permeability and subsequent NPE.[13,22,23,30] A lesion in the solitary tract nucleus also seems to alter the secretion of brain natriuretic peptide, which may also be involved in the pathogenesis of NPE.[6,7] These findings may explain why poor-grade patients with ruptured posterior circulation aneurysm were significantly more likely to sustain NPE compared with anterior circulation aneurysm, as previously reported.[25,26] The results of this study, shown in Fig. 1B and Table 2, are compatible with the previous findings. The logistic regression analysis also revealed that variables other than aneurysm location, including WFNS grade V SAH, were not associated with higher incidence of NPE-TCM.

Recent studies suggest that the presence of a lesion in and around the medulla oblongata may also be associated with TCM.[4,11,15] However, TCM occurs more frequently than NPE in the absence of a posterior fossa lesion,[18,19] and the relationship between aneurysm location and TCM has been studied less frequently. The possible anatomical difference in a causative brain lesion between NPE and TCM suggests that a sudden rise in serum catecholamine level induces TCM, whereas both rise in the serum catecholamine level and mechanical compression of the medulla are required for induction of NPE. Alternatively, patients with NPE-TCM may have suffered higher catecholamine exposure than those with only TCM. Measurement of serum catecholamine level in these patient groups may be helpful to evaluate these hypotheses. In this study, the majority of patients sustained poor-grade (grade IV or V) SAH, whereas previous studies had smaller percentages of poor-grade SAH patients.[3,24] We made every effort to obtain CT angiography, and finally investigated 100% of grade IV and 84% of grade V patients. This study found a higher incidence of ECG abnormality (Table 1) compared with previous reports, in which ST segment change and QTc prolongation was observed in 46% and 31%,[21] but may be explained by the difference in disease severity.

No evidence-based guidelines have indicated the optimal treatment modality or timing of intervention for SAH patients complicated with NPE-TCM. The patients are frequently hypotensive and hypoxic, despite the vigorous use of vasopressors and ventilation support, and coiling of the aneurysm has been advocated based on the potential risks of open surgery including general anesthesia.[10,14] On the other hand, aneurysm clipping under general anesthesia is feasible and safe in the acute phase for patients with NPE[34] or TCM.[19] In this study, only 8 of the 14 patients with NPE-TCM were hemodynamically and neurologically fit to undergo surgical or endovascular treatment, with 2 undergoing clipping surgery and 6 receiving coil embolization. Five of

the 8 patients were discharged with favorable outcomes, suggesting that treatment of patients with SAH complicated with NPE-TCM in the acute phase is feasible. With normovolemic fluid management, fatal vasospasm occurred only in 1 of the 8 patients who survived more than 7 days (Table 3). The efficacy and safety of triple-H therapy in patients with compromised cardiopulmonary function, which was not used in this study, is unclear and also needs to be studied. Interestingly, NPE seems to recede within 7 days of SAH onset in most surviving patients (Table 3).

Favorable outcomes for grade IV SAH patients treated endovascularly were similar to the results of previous studies.[10,14] However, whether patients considered unfit for coiling may be treated immediately or surgery should be deferred at least for 2 weeks remains unclear. Since the number of patients with SAH complicated with NPE-TCM is relatively small, a multi-center cooperative study may be required to clarify the issue.[17] The SAH grade on admission may be an important prognosticator, and so that outcome of grade IV patients was significantly better compared with that of grade V patients is not surprising. Most grade V patients died of primary brain damage incurred at the time of aneurysm rupture rather than cardiopulmonary dysfunction due to NPE-TCM. The cardiopulmonary dysfunction is transient and clinically manageable in most patients, but may become fulminant enough to cause cardiac arrest.[5] Aggressive circulatory intervention such as intra-aortic balloon pumping may be life-saving treatment in such circumstance.[1]

There are several limitations in this study. First, the diagnosis of TCM based on transthoracic ultrasonography was only qualitative, as cardiodynamic parameters, such as ejection fraction, were not routinely measured, so substantial variability was likely in the severity of TCM. Second, evaluation of patients with SAH for the presence of NPE-TCM was performed only in the emergency department, so a few patients with delayed onset NPE-TCM might have been missed.[27] Third, only 2 of the 16 patients with SAH complicated with NPE did not show signs of TCM. This study did not show how often SAH patients diagnosed initially with TCM sustained NPE, since transthoracic ultrasonography was performed only in patients presenting with clinical/radiological signs of NPE. Further investigation into the causal relationship between NPE and TCM is necessary.

In conclusion, patients with SAH complicated with NPE very frequently develop TCM, and we believe that routine transthoracic ultrasonography is essential for patients showing clinical/radiographic signs of NPE. Poor-grade SAH patients with ruptured posterior circulation aneurysm have elevated risk of developing NPE-TCM. In approximately half of patients with NPE-TCM, neither surgical nor endovascular intervention in the acute phase may be feasible. Grade IV patients have significantly better outcomes compared with grade V patients. Although endovascular obliteration of the ruptured aneurysm may be superior to clipping, the optimal treatment modality remains to be evaluated.

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Address reprint requests to: Joji Inamasu, MD, Department of Neurosurgery, Fujita Health University School of Medicine, 1–98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470–1192, Japan.
e-mail: ginamasu@aol.com