Clinical Features of Neurogenic Pulmonary Edema in Patients with Subarachnoid Hemorrhage

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■ OBJECTIVE: **Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by acute onset after central nervous system injury. Here, we investigated the clinical features of NPE in patients with subarachnoid hemorrhage (SAH).**

■ METHODS: **We retrospectively analyzed a total of 350 patients with SAH who were treated at our hospital from April 2014 to September 2017. Patient demographics, aneurysm size and location, clinical characteristics, and patient outcomes were reviewed and compared between an NPE and a non-NPE group.**

■ RESULTS: **Sixteen patients (4.6%) presented with NPE at admission. Ten of these (62.5%) recovered from NPE immediately, and ventilatory support was withdrawn within 2 days from onset. A univariate analysis showed that patients with NPE were younger ($P = 0.04$), had a higher rate of vertebral artery dissection ($P < 0.01$), more severe World Federation of Neurosurgical Societies (WFNS) grades ($P = 0.01$), and lower systolic blood pressure on admission ($P = 0.01$). A multivariate analysis revealed significant differences in the frequency of vertebral artery dissection (odds ratio 4.83, 95% confidence interval 1.50–15.56, $P < 0.01$) and in WFNS grades (odds ratio 3.73, 95% confidence interval 1.02–13.66, $P = 0.04$) between the groups. No significant group differences were found in other factors including heart rate, radiographic sign (Fisher grade), aneurysm size and location, blood sample tests on admission, and neurologic outcomes.**

■ CONCLUSIONS: **Vertebral artery dissection and severe WFNS grade on admission were confirmed as significant risk factors for NPE. However, neurologic outcomes at discharge did not differ between groups, suggesting that poor outcomes due to NPE could be reduced by appropriate diagnosis and treatment.**

INTRODUCTION

Neurogenic pulmonary edema (NPE) is known as a life-threatening severe complication occurring after central nervous disorders such as subarachnoid hemorrhage (SAH) and severe head injury.[1] NPE is defined as the sudden development of hypoxemic respiratory failure with radiographic findings of bilateral alveolar infiltrate, which cannot be attributed to other causes of acute respiratory distress syndrome.[2,3] The incidence rate of NPE after SAH has been reported to range from 2% to 31%.[4-8] Moreover, NPE after SAH is associated with worsened clinical outcomes, and the reported mortality of patients is 59%.[6,7,9,10] The pathogenic mechanism underlying NPE is thought to develop on the basis of rapid systemic sympathetic activity, but this has not been clarified.[3,11] Epidemiologic data on NPE are scarce and often based on case reports or studies with low numbers of patients.[3] The aim of this study was thus to investigate the frequency, clinical features, and prognosis of NPE, by assessing 350 cases of SAH at our institution.

Key words
- Aneurysm
- Central nervous system injury
- Neurogenic pulmonary edema
- Subarachnoid hemorrhage
- Vertebral artery dissection
- WFNS grade

Abbreviations and Acronyms
CT: Computed tomography
mRS: Modified Rankin Scale
NPE: Neurogenic pulmonary edema
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurosurgical Societies

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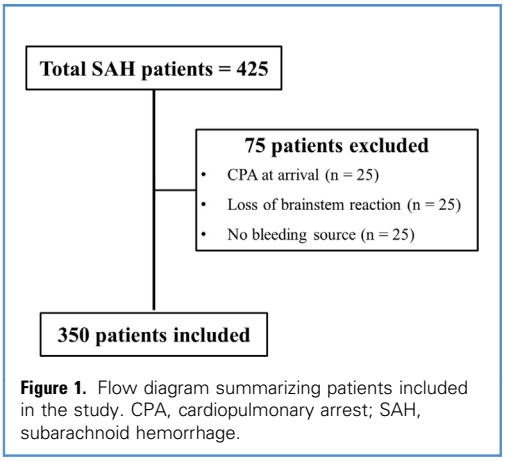

Figure 1. Flow diagram summarizing patients included in the study. CPA, cardiopulmonary arrest; SAH, subarachnoid hemorrhage.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of 425 patients with SAH who were admitted to our hospital from April 2014 to September 2017. Patients who presented with cardiopulmonary arrest ($n = 25$) or loss of brainstem reaction ($n = 25$) on admission were excluded. In addition, patients without an apparent bleeding source of SAH ($n = 25$) were also excluded. Finally, 350 patients were included in this study (Figure 1). Patient demographics, aneurysm size and location, clinical characteristics, and patient outcomes were reviewed and compared between an NPE and a non-NPE group. The requirement for informed consent was waived due to the retrospective nature of the study. The Institutional Review Board of Saitama Medical University International Medical Center approved all aspects of this study (application number 18–282).

Variables

We defined NPE as diffuse pulmonary infiltrates observed on chest radiograph without heart or kidney failure, as determined via blood tests and the patient's medical history on admission. No patient received vasodilators during/at the time of the diagnosis. More than 2 attending doctors were in charge of diagnosing NPE, and the echocardiographic examination and computed tomography (CT) scan of the lung were performed accordingly. All patients were diagnosed with SAH by CT scans, and the aneurysm location was identified by CT angiography or catheter cerebral angiography. Clinical severity was assessed using the World Federation of Neurosurgical Societies (WFNS) grading system on admission, and WFNS grades 3–5 were defined as severe SAH. Radiologic severity was assessed with the Fisher score. Neurologic outcomes were evaluated with the modified Rankin Scale (mRS) at discharge.

Statistical Analysis

Demographic and clinical characteristics were compared via univariate analysis using chi-squared tests, the Fisher exact test, Student t-tests, and the Mann-Whitney U test between groups with and without NPE. After the univariate analysis, a multivariate regression analysis was conducted to identify independent factors related to NPE. Factors with $P < 0.1$ were selected for a stepwise multivariate regression analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were obtained from the regression analysis. $P < 0.05$ was considered to be statistically significant. Data were analyzed using IBM SPSS Statistics (version 24; IBM Corp, Armonk, New York, USA).

RESULTS

Out of 425 patients with SAH, 350 patients who underwent microsurgical or endovascular repair at our institution were included. Demographics and clinical characteristics of the patients are shown in Table 1. NPE was observed in 16 of these 350 patients (4.6%). The univariate analysis revealed significant differences between the NPE and non-NPE group in mean age, systolic blood pressure on admission, the frequency of vertebral artery dissection on admission, and WFNS grades. Patients with NPE were treated mainly with ventilator management with high positive end-expiratory pressure and control of fluid volume, and no significant differences between the groups with and without NPE were observed regarding blood sample data and clinical outcomes at discharge. The multivariate analysis revealed significant group differences in WFNS grades (OR 3.73, 95% CI 1.02–13.66, $P = 0.04$) and the frequency of vertebral artery dissection (OR 4.83, 95% CI 1.50–15.56, $P < 0.01$) (Table 2). Table 3 presents a summary of the 16 patients with NPE. Notably, 10 patients (62.5%) could withdraw from the respirator within 2 days from onset, and all except 1 could withdraw within 1 week. Finally, 8 patients (50%) achieved good outcomes (mRS scores between 0 and 3 at discharge).

DISCUSSION

NPE is known to be a severe complication after central nervous system insults such as SAH and head injuries and is considered to be a result of sympathetic stimulation by catecholamine release.[5,12,13] NPE after SAH has been reported to occur in 2%–31% of cases,[4-8] and in our study, 4.6% of patients with aneurysmal SAH had NPE, which is well within the reported range.

Previous studies showed that the incidence of NPE is significantly higher in patients with ruptured aneurysms of the posterior circulation, resulting in acute intracranial pressure elevation near the bulbar area.[6,11] Other authors reported that the triggers of NPE development are insults in the hypothalamus, brainstem, and cervical nucleus.[14,15] In our analysis, vertebral artery dissection on admission (dissecting aneurysms in all cases) appeared as a predictor of NPE. Furthermore, although there was no significant difference in the distribution of aneurysm locations between the NPE and non-NPE group, we observed a higher tendency for posterior circulation aneurysms in patients with NPE than in patients without NPE (37.4% vs. 19.2%). Our data support the notion that posterior circulation aneurysms could be a factor for the development of NPE.

Also, severe SAH grade on admission is considered to be related to the development of NPE, presumably due to the increased intracranial pressure and activation of sympathetic nerve

Table 1. Univariate Analysis Between Patients with and without Neurogenic Pulmonary Edema (NPE)

Variable	Total (n = 350)	NPE Group (n = 16)	Non-NPE Group (n = 334)	*P* Value
Mean age ±SD, years	64.3 ± 14.4	61.8 ± 13.6	65.0 ± 14.2	0.04
Female sex, number (%)	233 (66.6%)	11 (68.8%)	222 (66.5%)	0.85
CTR ±SD, %	53.7 ± 4.8	53.9 ± 4.4	53.6 ± 5.0	0.96
sBP ±SD, mm Hg	162.4 ± 37.6	151.5 ± 42.8	166.9 ± 38.0	0.01
Heart rate ±SD,/min	82.4 ± 18.2	85.9 ± 14.4	82.2 ± 18.2	0.58
Blood sample data				
Cr ± SD, mg/dL	0.69 ± 0.59	0.62 ± 0.20	0.71 ± 0.67	0.66
Na (min) ± SD, mEq/L	134.3 ± 8.1	134.3 ± 2.8	134.4 ± 3.9	0.74
Na (max) ± SD, mEq/L	147.2 ± 7.1	150.1 ± 6.5	146.2 ± 4.8	0.33
K (min) ± SD, mEq/L	3.1 ± 0.4	3.0 ± 0.3	3.1 ± 0.4	0.50
K (max) ± SD, mEq/L	4.6 ± 0.5	4.6 ± 0.4	4.5 ± 0.5	0.95
Albumin ±SD, g/dL	2.6 ± 0.6	2.5 ± 0.4	2.7 ± 0.6	0.18
Imaging findings				
With ICH, number (%)	94 (26.9)	4 (25.0)	90 (26.9)	0.56
Aneurysm size ±SD, mm	6.0 ± 3.4	4.8 ± 1.5	6.0 ± 3.3	0.27
Aneurysm location, number (%)				0.91
ACA	115 (32.9)	3 (18.8)	112 (33.5)	
MCA	62 (17.7)	4 (25.0)	58 (17.4)	
ICA	103 (29.4)	3 (18.8)	100 (29.9)	
VA-BA	70 (20.0)	6 (37.4)	64 (19.2)	
VA dissection, number (%)	27 (7.7)	5 (31.3)	22 (6.6)	<0.01
Fisher group 3–4, number (%)	289 (82.6)	15 (93.8)	274 (82.0)	0.20
Complications, number (%)				
Symptomatic vasospasm	45 (12.9)	2 (12.5)	43 (12.9)	0.66
Shunt dependent hydrocephalus	53 (17.7)	2 (12.5)	60 (17.9)	0.44
Medical history, number (%)				
Diabetes	24 (6.9)	0 (0.0)	24 (7.2)	0.31
Hypertension	149 (42.6)	4 (25.0)	145 (43.4)	0.14
WFNS grade 3–5, number (%)	175 (50.0)	13 (81.3)	162 (48.5)	0.01
mRS at discharge, number (%)				0.36
Good (mRS 0–3)	136 (38.9)	8 (50.0)	204 (61.1)	
Poor (mRS 4–6)	212 (61.1)	8 (50.0)	128 (38.3)	

SD, standard deviation; CTR, cardiothoracic ratio; sBP, systolic blood pressure; Cr, creatine; Na, sodium; mEq, milliequivalent; K, potassium; ICH, intracerebral hemorrhage; ACA, anterior cerebral artery; BA, basilar artery; MCA, middle cerebral artery; ICA, internal carotid artery; VA, vertebral artery; WFNS, World Federation of Neurosurgical Societies; mRS, modified Rankin Scale.

stimulation.[7,15,16] In addition, Inamatsu et al[12] investigated plasma catecholamine (epinephrine and norepinephrine) levels of patients with SAH within 48 hours from onset and revealed that plasma norepinephrine levels were correlated with NPE. In line with such reports, our analyses revealed severe SAH grade on admission as another factor predicting the development of NPE, although plasma catecholamine levels were not measured. The precise mechanisms of NPE development have not been clarified,[3,11] but rapid elevation of intracranial pressure and systemic sympathetic activity could be a key factor for the development of NPE.

Several studies reported that arterial pressure was higher in patients with NPE than in patients without NPE[9,14]; however, in this study, systolic blood pressure was lower in patients with

Table 2. Multivariate Analysis of Risk Factors for Neurogenic Pulmonary Edema

Variables	Odd Ratio	95% CI	*P* Value
Age	0.97	0.93–1.01	0.11
WFNS grade 3–5	3.73	1.02–13.66	0.04
VA dissection	4.83	1.50–15.56	<0.01

WFNS, World Federation of Neurosurgical Societies; VA, vertebral artery.

NPE than in patients without NPE. It has been suggested that vascular hyperpermeability caused by catecholamine release leads to intravascular hypovolemic or transient disruption of cardiac function via cardiomyopathy and might cause both higher and lower arterial pressure. In any case, abnormal blood pressure could be induced by NPE, rather than causing NPE. Therefore we excluded the factor "lower systolic blood pressure" from the multivariate analysis.

There have been sporadic studies reporting that the development of NPE is associated with a worsened clinical prognosis.[6,7,9,10] In 1 study, the fatality rate for the onset of neurogenic pulmonary edema was as high as 59%, and only 23% of affected patients achieved a good prognosis.[7] Patients with NPE at our institution are treated intensively with adequate ventilator management and control of fluid volume, and no significant differences between the groups with and without NPE were observed regarding neurologic outcomes at discharge, suggesting that patient morbidity and mortality due to NPE might be reduced by accurate diagnosis and appropriate treatment.

This study has several limitations. First, patient data were collected retrospectively. Secondary, the exclusion of patients with cardiopulmonary arrest might have led to an overestimation of good outcomes; however, as cardiopulmonary resuscitation was performed in such cases, we were not able to evaluate NPE appropriately and could therefore not include them in our analyses. Thirdly, catecholamine release induced by SAH has been reported to lead to left heart failure via increased preload and afterload, resulting in cardiomyopathy.[7,17] Due to the neurogenic overstimulation of the sympathetic nervous system, patients with SAH complicated with NPE tend to develop takotsubo-like cardiomyopathy.[17] However, we were unable to investigate echocardiographic findings in some patients with NPE. Although no patient in the current study had a past medical history of heart failure, cardiac functions and body fluid volumes on admission need to be evaluated to clarify the relationship between NPE and cardiac dysfunction.

Table 3. Summary of 16 Patients with Neurogenic Pulmonary Edema

Case Number	Age/ Sex	WFNS Grade	sBP (mm Hg)	Heart Rate (/min)	Cr (mg/ dL)	Na (Min/Max) (mEq/L)	K (Min/Max) (mEq/L)	CTR (%)	Location/ Size (mm)	With ICH	Fisher Group	Withdraw from Respirator (day)	mRS at Discharge
1	78/F	3	160	85	0.53	128/146	3.2/4.2	60	ICA-PCoA/5.0	-	3	2	2
2	43/M	5	214	84	0.92	136/149	3.1/5.1	49	VA dissection	-	3	6	5
3	67/F	4	91	88	0.53	132/148	2.7/4.7	55	MCA/6.0	+	3	2	3
4	55/F	5	239	77	0.47	137/153	2.5/5.0	56	MCA/6.3	+	3	2	5
5	70/F	2	157	110	0.73	134/160	3.0/4.6	53	MCA/6.0	-	3	1	4
6	76/F	5	101	89	0.3	135/155	2.9/4.6	55	MCA/5.1	+	4	1	5
7	40/F	4	148	98	0.66	138/168	2.8/4.0	53	ACoA/2.7	+	3	17	6
8	46/F	5	171	76	0.66	137/144	3.2/4.5	57	ACoA/2.0	-	3	2	1
9	69/M	4	138	67	0.79	134/155	3.2/4.5	52	ACoA/6.0	-	3	5	4
10	39/M	4	122	58	0.88	134/143	2.7/4.5	49	VA dissection	-	3	2	2
11	87/F	4	138	80	0.57	135/192	2.8/4.1	64	VA-PICA/3.8	-	3	4	6
12	44/M	5	100	80	0.8	131/142	3.5/5.4	51	VA dissection	-	3	7	4
13	58/M	3	136	80	0.93	134/146	2.7/4.0	53	ICA-PCoA/5.0	-	3	1	1
14	44/F	3	113	60	0.57	137/144	3.5/4.4	54	ICA/7.0	-	3	1	0
15	42/F	2	110	103	0.51	135/142	3.4/5.4	45	VA dissection	-	3	2	3
16	54/F	2	106	102	0.55	136/145	3.2/4.1	55	VA dissection	-	2	5	1

WFNS, World Federation of Neurological Societies; SBP, systolic blood pressure; Cr, creatine; Na, sodium; K, potassium; CTR, cardiothoracic ratio; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; ICA, internal carotid artery; PCoA, posterior communicating artery; VA, vertebral artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; PICA, posterior inferior cerebellar artery.

CONCLUSION

This study found a rate of 4.6% of NPE in a sample of patients with SAH. Vertebral artery dissection and severe WFNS grade on admission appeared to be predictive factors for NPE. NPE has been suggested to be a severe complication of SAH and to be related to mortality, but we found no differences in outcomes at discharge between patients with and without NPE after appropriate multidisciplinary treatment.

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