Prevalence of Takotsubo Syndrome among Patients Admitted to an Emergency Department

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Aim : Takotsubo syndrome (TTS) is identified in 1-3 % of patients with suspected acute coronary syndrome and is a complication of various diseases. This study aimed to clarify the prevalence and clinical characteristics of TTS among patients admitted to the emergency department of a tertiary hospital.

Methods : We conducted a post-hoc analysis of a single-center prospective observational study of all patients admitted to our emergency department between April 2003 and March 2014. The diagnosis of TTS was based on the Mayo diagnostic criteria.

Results : Among 14,178 patients admitted, TTS was diagnosed in 33 patients (male, 36 % ; median age 76 (interquartile range, 70-80) years), with a prevalence rate of 0.23 %. The cases without preceding physical illness included 40 % of patients (the primary TTS group), and the cases with preceding physical illness included 60 % of patients (the secondary TTS group). Chest discomfort was the presenting symptom in only 25 % of patients in the secondary TTS group compared to 92 % in the primary TTS group ($p < 0.001$). The Acute Physiology and Chronic Health Evaluation II scores were higher in the secondary TTS group than in the primary TTS groups ($p = 0.002$)

Conclusions : The prevalence of TTS among patients admitted to the emergency department was 0.23 %. TTS triggered by a physical illness formed a high percentage, and in the majority of these cases chest symptoms were not presenting complaints. Nevertheless, physicians should screen for TTS as part of the assessment of patients admitted to the emergency department. *Shinshu Med J 70 : 39—46, 2022*

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Key words : Takotsubo syndrome, emergency department, chest symptom

I Introduction

Takotsubo syndrome (TTS), which was first described in 1990, is an acute, reversible disorder of the heart that is characterized by left ventricular dysfunction[1)-3)]. Chest pain and dyspnea, mimicking an acute coronary syndrome, are common clinical manifestations of TTS. In addition, the onset of TTS is often preceded by an emotional or physical trigger[3)4)]. Although TTS is generally transient in nature, requiring only supportive management[4)], complications of TTS, such as heart failure, arrhythmias, and some hemodynamic instability, can be life-threatening or prolong hospital stay[5)6)]. Menopause and severe emotional or physical stress are known risk factors for TTS[2)-7)], although absence of these factors does not preclude the diagnosis of TTS. Therefore, improved understanding of TTS is essential for diagnosis and treatment.

TTS complicates the clinical course of various diseases. However, few reports have evaluated the preva-

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lence of TTS among patients hospitalized for an acute condition in the United States and among those admitted to the intensive care unit (ICU)[7)-10)]. It is possible that TTS might be specifically prevalent among patients presenting to the emergency department. Considering the few studies that have addressed this issue, we aimed to clarify the prevalence of TTS among patients admitted to the emergency department of a tertiary hospital, and to describe the clinical characteristics of TTS among these patients.

Ⅱ Methods

A Study design

The study was approved by the Shinshu University School of Medicine Institutional Review Board and was conducted in accordance with the amended Declaration of Helsinki.

This was a post-hoc analysis of a prospective observational study of all patients admitted to the emergency department of Shinshu University hospital between April 2003 and March 2014. Shinshu University hospital is an academic tertiary hospital located in the Matsumoto region (area 1,868 km^2, 430,000 residents) and is also the base hospital for the physician-staffed helicopter emergency medical service for Nagano prefecture (area 13,560 km^2, 2 million residents)[11)].

B Procedures

All patients presenting with one or more of the following findings underwent echocardiography to screen for TTS : chest symptoms, abnormal electrocardiogram (ECG), pulmonary edema, or hypotension of unknown etiology. Unless contraindicated, all patients underwent coronary angiography. The diagnosis of TTS was made based on the Mayo diagnostic criteria[4)], as follows : (1) transient left ventricular systolic dysfunction, which is typically regional and extends beyond a single epicardial coronary distribution ; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, noting that the diagnosis of takotsubo cardiomyopathy can still be made in the presence of coronary disease so long as the abnormal contractile motion of the heart wall is not in the distribution of the coronary disease ; (3) new abnormality on the ECG, either ST-segment elevation and/or T-wave inversion, or a modest elevation in cardiac troponin ; and (4) absence of pheochromocytoma, myocarditis, or subarachnoid hemorrhage.

These data were then used to estimate the prevalence of TTS among patients admitted to our emergency department. To describe the range of clinical features of TTS, patients with a positive diagnosis were divided into two groups according to the existence of preceding physical illness : the Primary TTS group, in which TTS was the main event of hospitalization, and the Secondary TTS group, in which another physical illness was the main cause of hospitalization and TTS was recognized as a complication. Clinical features were compared between these two groups.

C Statistical analyses

Continuous variables are reported as median (interquartile range), with categorical variables reported as count and percentage. Between-group comparisons of continuous variables were performed using the t-test for normal and non-normal variable distributions, and a chi-squared analysis (χ^2) was used to compare categorical variables. Analyses were performed using IBM SPSS Statistics software (version 22), with a p-value$<$0.05 considered significant.

Ⅲ Results

Between 2003 and 2014, 14,178 patients were admitted to our emergency department, with TTS diagnosed in 33 cases, with a prevalence rate of 0.23 %. Of the 33 cases, 28 underwent coronary angiography. Although 3 cases had shown significant stenosis and received percutaneous coronary intervention, the distribution of asynergy did not correspond to the dominant region of the coronary artery with significant stenosis in each case. A coronary spasm was not observed in any case. In addition, 5 cases did not undergo coronary angiography owing to the patients' conditions (head injury, cardiopulmonary arrest after epidural anesthesia, pan peritonitis, snake bite, airway obstructions). ECG abnormalities were observed in all the cases at TTS diagnosis : ST elevation (39 %), T

wave inversion (48 %), abnormal Q wave (24 %), and poor R wave progression (18 %). Autumn is the most prominent season for the onset of TTS, as follows : spring (21 %), summer (15 %), autumn (39 %), and winter (24 %). The baseline characteristics of these patients are summarized in **Table 1**. Among this group, 64 % were female and 76 % had a history of hypertension. A physical triggering event was identified in 20 of these 33 cases (the secondary TTS group), and the other 13 cases were classified in the Primary TTS group. The triggering events among patients in the Secondary TTS group included the following : hypoglycemic coma ; acute on chronic renal failure induced by acute diarrhea ; epilepsy ; bacterial infection, including sepsis, acute upper respiratory tract infection ; bowel obstruction ; asthma attack ; superior mesenteric artery obstruction ; head injury ; snake bite ; airway obstruction ; pan peritonitis ; elective hepatectomy ; and epidural anesthesia. The triggering events among the Primary TTS group were emotional stress (6 cases) or unknown (7 cases) ; emotional stress included inter-personal quarrels, the death of a spouse, and work-related stress. The baseline characteristics of patients in each of these 2 groups are summarized in **Table 2**.

The clinical course for each of the 2 groups is summarized in **Table 3**. Complaints of chest symptoms were more frequent in the Primary TTS groups (92 %) than in the Secondary TTS group (25 %) ($p < 0.001$; **Fig. 1**). Therefore, while chest symptoms were the clinical clue for TTS in most of patients in the Primary TTS group, the diagnosis for the Secondary TTS group was based on objective findings of pulmonary edema, ECG abnormality, arrhythmia, or un-

Table 1 Baseline characteristics of patients with TTS

Characteristics	
Number of patients	33
Age (years)	76 (70–80)
Female, n (%)	21 (64)
BMI (kg/m^2)	22.4 (19.2–25.1)
Medical history, n (%)	
Hypertension	25 (76)
Dyslipidemia	10 (30)
Diabetes mellitus	8 (24)
Smoking	4 (12)
Psychiatric disease	3 (9.1)
Cardiac failure	6 (19)
Medication on admission, n (%)	
Beta-blocker	3 (9)
ACE inhibitor/ARB	20 (61)
Calcium channel blocker	14 (42)
Diuretics	11 (33)
Steroid	3 (9)

BW, Body Weight ; BMI, Body Mass Index ; ACE, Angiotensin-converting Enzyme ; ARB, Angiotensin II Receptor Blocker

Table 2 Baseline characteristics of each TTS group

Variable	Groups		P-value
	Primary (n = 13)	Secondary (n = 20)	
Age (years)	77 (70–80)	76 (70–81)	0.446
Female, n (%)	10 (77)	11 (55)	0.278
BW (kg)	52.0 (42.5–60.2)	51.5 (45.9–57.8)	0.824
BMI (kg/m^2)	24.1 (20.2–25.9)	21.0 (19.2–24.3)	0.877
Medical history, n (%)			
Hypertension	12 (92)	13 (65)	0.108
Dyslipidemia	2 (15)	8 (40)	0.245
Diabetes mellitus	1 (8)	7(35)	0.108
Smoking	1 (8)	3 (15)	1
Psychiatric disorder	2 (15)	1 (5)	0.547
Cardiac failure	1 (8)	5 (25)	0.361
Medication on admission, n (%)			
Beta-blocker	0 (0)	3 (15)	0.261
ACE inhibitor/ARB	10 (77)	10 (50)	0.159
CCB	5 (38)	9 (45)	1
Diuretics	3 (23)	8 (40)	0.456
Steroid	0 (0)	3 (15)	0.261

BMI, Body Mass Index ; ACE, Angiotensin-converting Enzyme ; ARB, Angiotensin II Receptor Blocker ; CCB, Calcium channel blocker

Table 3　Presentation and clinical course of each group of TTS

Variable	Groups		P-value
	Primary (n = 13)	Secondary (n = 20)	
Chest symptoms on presentation, n (%)	12 (92)	5 (25)	＜0.001
Chest pain	10 (77)	2 (10)	＜0.001
Dyspnea	2 (15)	3 (15)	1
No chest symptom	1 (8)	15 (75)	＜0.001
First clue to diagnosis,n (%)			
Pulmonary edema	0	6 (30)	0.060
ST change in ECG	2 (15)	5 (25)	0.676
Arrhythmia	0	2 (10)	0.508
Hypotension	0	2 (10)	0.508
APACHE Ⅱ score	9 (7-11)	17 (14-21)	0.002
Peak CK-MB (IU/L)	29 (17-51)	24 (14-34)	0.135
CRP (mg/dL)	0.4 (0.2-1.3)	4.8 (0.1-11.7)	0.006
BNP (pg/mL)	234.0 (138-443)	858 (527-1577)	0.539
Anatomical variants of TTS, n (%)			
Apical type	13 (100)	20 (100)	***
Non-apical type	0	0	***
Ejection Fraction at diagnosis	45 (40-63)	†40 (36-49)	0.198
Treatment device, n (%)			
Mechanical ventilation	2 (15)	11 (51)	0.032
IABP	0	0	***
Temporary pacing	1 (8)	2 (10)	1
Hospital stay	11 (8-15)	25 (22-34)	0.018
ICU stay	5 (3-6)	12 (4-25)	0.006
Complication, n (%)			
Arrhythmia	2 (15)	10 (50)	0.067
Embolism	0	0	***
Cardiac rupture	0	0	***
Death, n (%)	0	1 (5)	1

ECG, Electrocardiogram ; APACHE, Acute Physiology and Chronic Health Evaluation ; CK, Creatine Kinase ; CRP, C-Reactive Protein ; BNP, Brain Natriuretic Peptide ; IABP, Intra-aortic Balloon Pumping ; ICU, Intensive Care Unit
† Three cases were excluded due to missing values.

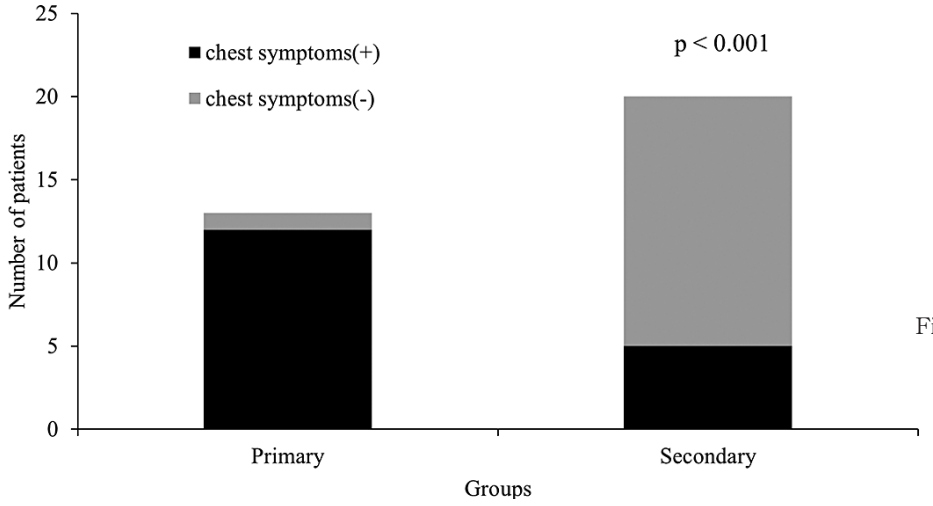

Fig. 1　The number of patients, *with* and *without* chest symptoms, in each of the two TTS groups

explained hypotension. The Acute Physiology and Chronic Health Evaluation (APCHE) II scores were higher in the Primary TTS group than in the emotional and unknown trigger groups, as was the length of ICU and hospital stay. The occurrence of arrhythmia (including torsades de pointes, complete atrioventricular block, atrial fibrillation, bradycardia, ventricular tachycardia, paroxysmal supraventricular tachycardia,

and multifocal premature ventricular contraction) also tended to be more frequent in the Secondary TTS group. Temporary pacing was required for 3 cases (2 cases for complete atrioventricular block and 1case for torsades de pointes), while the other cases were only followed up. One patient in the physical group died due to multiple organ failure subsequent to obstruction of the superior mesenteric artery.

Ⅳ Discussion

The main findings of our study were as follows : (1) a prevalence rate of TTS of 0.23 % among patients admitted to a tertiary emergency department ; (2) triggering of TTS by physical illness (the Secondary TTS group) in 60 % of patients ; and (3) absence of chest symptoms (pain and dyspnea) in the majority of cases of TTS triggered by physical illness. To our knowledge, this is the first report regarding the prevalence of TTS among a general group of patients admitted to the emergency department.

TTS was first described in Japan in 1990[1] and is characterized by a transient regional systolic dysfunction of the left ventricle, with four types of anatomical variants based on the abnormality in the motion of the left ventricular wall[12] : apical type, mid-ventricular type, basal type, and focal type. Although the practical significance of these anatomical differences has not been fully clarified, it is possible that each represents the different time periods needed for recovery of the affected left ventricular segments[13]. Pathophysiologically, TTS is related to sympathetic activation and catecholamine toxicity[10)13)].

The prevalence rate of TTS among patients with suspected acute coronary syndrome is 1-3 %[4)-7)14)15)]. But the prevalence of TTS among the general population, as well as among the general population of patients admitted to the emergency department, has been unclear. Deshmukh et al.[7] reported a prevalence rate of TTS of 0.02 % among all acute hospitalizations in the United States. Their data were collected from the inpatient care database of nearly 1,000 hospitals in the United States. Specifically, 6,837 patients among 33,506,402 hospitalizations received a primary diagnosis of TTS, as coded by the International Classification of Diseases (9th revision). The prevalence of TTS in our study was about 10-fold higher than the rate reported by Deshmukh et al. The following two reasons might provide an explanation for this discrepancy. First, Deshmukh et al. studied all hospitalizations, including non-emergency patients, while our study was performed at a tertiary emergency department ; thus, the severity and the urgency of illness were higher among our study group than the patients in Deshmukh et al.'s study. As such, it is possible that our study patients were in a more stressful situation. Second, in our study, all patients with chest symptoms, abnormal ECG, pulmonary edema, or hypotension of unknown etiology underwent an echocardiogram assessment. In this way, almost all patients with TTS would have been identified ; in contrast, Deshmukh et al. calculated the prevalence rate of TTS from a database of patients in daily practice. As a complication of various physical illnesses, TTS would be especially difficult to diagnose in clinical practice. Thus, a considerable number of patients with TTS may have been overlooked in Deshmukh et al.'s study[7]. In ICUs, the prevalence rate of TTS has been reported to range between 0.9 % up to 26 %[8)9)16)17)]. More recently, it has been suggested that TTS may be associated with severe conditions that cause high sympathetic activity, such as sepsis, respiratory failure and neurological emergencies[10)15)18)]. As such, TTS may be more frequent among patients admitted to the ICU than in general emergency settings. Because TTS can adversely influence the clinical course of primary diseases, physicians should recognize the prevalence of TTS in each clinical setting and diagnose it as soon as possible.

TTS has recently been classified into primary and secondary subtypes. In primary TTS, patients seek care for acute cardiac symptoms[18]. By comparison, secondary TTS develops in patients who are already hospitalized for another problem, such as perioperative complications, trauma, or other medical conditions. Our study also classified TTS along with these subtypes. As the study was performed in the emergency department, most cases of secondary

TTS were diagnosed upon admission among patients in the physical group.

A 2014 meta-analysis[19] estimated a prevalence rate of primary TTS of 60 %, with a 40 % rate of secondary TTS. Among our study group, the rate of secondary TTS was higher than this, at 60 %. It might be that this higher prevalence rate of secondary TTS reflects our increased awareness and, thus, diagnosis of this condition.

The high prevalence of TTS among post-menopausal women has been well documented[18]. In their review of patients diagnosed with TTS among 31 heart institutes in Germany and Austria, Schneider et al.[20] reported that 91 % of patients with TTS were women. Moreover, physical stress as a cause of TTS was more frequent in men (57 %) than in women (30 %), with women experiencing greater emotional triggers or unknown triggers of TTS. This is consistent with our findings. In our study group, 64 % of patients were women. In the Primary TTS group, 77 % of patients were women, with TTS in men commonly having a physical trigger.

Previous studies have reported chest pain as being the presenting symptom in 41-75 % of TTS cases[12][19][21], this rate being consistent with our rate of 51 % for our study group. Of note was that chest pain was the presenting symptom in only 25 % of patients in the Secondary TTS group. The reason for this discrepancy between groups is unclear, although the majority of patients in the Secondary TTS group had a critical physical illness, including some with altered consciousness. As these cases were critical, the perception of chest pain may have been attenuated by the health condition. For example, among the patients with pulmonary edema, we observed one case each of hypoglycemic coma (unable to complain), epilepsy (unable to complain), and acute obstructive suppurative cholangitis (chest discomfort would be masked by other symptoms such as upper abdominal pain). Therefore, while chest symptoms were the clinical clue for a diagnosis of TTS in the majority of patients in the Primary TTS group, objective findings (such as pulmonary edema, hypotension, ECG abnormality, or arrhythmia) were the clinical clue for diagnosis in the majority of cases in the Secondary TTS group. Therefore, TTS should be considered, with a high index of possibility, among patients presenting with these symptoms.

Early recognition of TTS among emergency patients is important when we consider the potential for TTS to complicate the clinical course of a wide range of illnesses. Thus, echocardiography should be repeated in patients presenting with an abnormal ECG, pulmonary edema, or hypotension of unknown etiology, which are known complications of TTS. In addition, point-of-care ultrasonography, which consists of a focused cardiac ultrasound examination performed by a physician at the time of the physical examination, would provide a feasible solution for early recognition of ultrasound-specific signs of TTS[22] and thus, screening for TTS.

A previous study reported a higher APCHE II score among patients with TTS associated with acute medical stress or surgery/procedure than among those with an emotional stress triggering event[23]. Similarly, patients in the Secondary TTS group had significantly higher APACHE II scores than patients in the Primary TTS group in our study. Furthermore, the occurrence of arrhythmia was more frequent in the Secondary than in the Primary TTS group. Therefore, cardiac damage by TTS is likely to be greater in the secondary than in the primary groups due to higher sympathetic activity and catecholamine levels. It has been reported that TTS increases the risk of mortality in the ICU[16][23][24]. Thus, it is possible that emergency patients with physical illness and concurrent TTS would be at an increased risk of a poor clinical outcome, particularly with a delay in TTS diagnosis. Moreover, early diagnosis of TTS is essential for proper hemodynamic management and could improve the prognosis of emergency patients.

V Limitations

The limitations of our study were as follows. First, this was a single-center study performed in a tertiary emergency department. Although we included almost all patients, regardless of the nature of the medical

condition, the severity of illness could have been higher in our study population of patients admitted to the emergency department than in primary care facilities. Thus, the frequency of TTS could vary between facilities according to the severity of patients admitted to their services. Second, the number of patients with TTS in each group was relatively small. Thus, differences in clinical features of primary and secondary TTS could not be fully clarified. A multicenter study would be ideal for the population and averaging the severity ; however, it is not feasible for all suspected patients to be screened TTS with echocardiography to the same high quality among different hospitals.

Ⅵ Conclusions

The prevalence of TTS among patients admitted to a tertiary care center was 0.23 %. The majority of patients with TTS triggered by physical illness (secondary TTS) did not present with chest symptoms, with objective findings, such as pulmonary edema and ECG abnormality, being major clues to TTS diagnosis. Therefore, physicians should consider screening for TTS in the assessment of patients admitted to the emergency department.

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