A Comparative Retrospective Study of Patients with Takotsubo Syndrome and Acute Coronary Syndrome

Gassan Moady MD MPH[1,2], Shelly Vons MD[2], and Shaul Atar MD[1,2]

[1]Department of Cardiology, Galilee Medical Center, Nahariya, Israel
[2]Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

ABSTRACT Takotsubo syndrome (TTS) is a non-ischemic cardiomyopathy characterized by an acute reversible left ventricular dysfunction with typical apical ballooning, usually with subsequent complete spontaneous recovery. TTS shares several features with acute coronary syndrome (ACS), including clinical presentation, ECG changes, and elevated troponin.

Objectives: To identify different features that may help differentiate between TTS and ACS with presentation based on presenting symptoms and physical examination.

Methods: We compared 35 patients who TTS had been diagnosed with 60 age- and sex- matched patients with ACS (both ST and non-ST segment elevation myocardial infarction) who were hospitalized in Galilee Medical Center through 2011-2015.Basic characteristics and clinical features of the two groups were compared using appropriate statistical tests.

Results: Of the patients with TTS, 21 (60%) reported an emotional trigger (60%) before admission, although they did not have increased prevalence of psychiatric disease compared to ACS patients (5.7% vs. 5%, $P = 0.611$). There was no difference in the type of chest pain or accompanied symptoms between the groups. Of notice, ECG changes in the TTS group were prominent in the anterior leads, and the patients presented with higher heart rate (86 ± 17 vs. 79 ± 15, $P = 0.029$) and lower systolic blood pressure (129 ± 26 vs. 142 ± 30, $P = 0.034$) on admission compared to the ACS group.

Conclusions: There was no reliable feature that could distinguish TTS from ACS based on clinical presentation. TTS should always be in the differential diagnosis in patients with acute chest pain, especially in elderly women.

IMAJ 2021; 23: 107–110

KEY WORDS: acute coronary syndrome (ACS), angiography, biomarker, echocardiography, Takotsubo syndrome (TTS)

Takotsubo cardiomyopathy (TTS) is characterized by acute reversible left ventricular dysfunction with typical wall motion abnormality (apical ballooning) without evidence for epicardial obstructive coronary artery disease [1]. About 87% of the affected patients are women with a mean age of 67–70 years, usually with preceding emotional trigger [2]. TTS should always be in the differential diagnosis in patients presenting with chest pain suspected to be from coronary origin. Many criteria have been proposed for TTS diagnosis, but the most commonly used are the revised Mayo Clinic diagnostic criteria and the international Takotsubo diagnostic criteria. These criteria are largely based on the following findings: 1) Transient left ventricular dysfunction with the typical apical ballooning pattern, 2) Absence of obstructive coronary artery disease or acute plaque rupture on angiography (the presence of atherosclerotic disease should not exclude Takotsubo, as the wall motion abnormalities in TTS usually extend beyond the territory of the involved coronary artery, 3) New electrocardiographic abnormality (ST segment elevation or T wave inversion in the anterior leads) or cardiac troponin elevation, 4) Absence of pheochromocytoma or myocarditis [3]. In order to confirm the diagnosis, a repeat echocardiography is needed with demonstration of complete normalization of cardiac shape and function, usually within 3-6 months. The pathophysiology of TTS is not fully understood, but several theories have been proposed to explain the underlying mechanisms. High levels of plasma catecholamine and neuropeptides have been reported in patients with TTS [4], although TTS has been reported also in patients after bilateral adrenalectomy with low serum catecholamine levels [5]. The high catecholamine level may induce intracellular signal switch from stimulatory G(s) to inhibitory G(i) protein signaling via the β2-adrenoceptor, leading to negative inotropy and resultant left ventricular contractile dysfunction that can explain the apical forms of Takotsubo syndrome where beta-adrenergic receptors are predominant [6]. The catecholamine surge after stress episode that is responsible for regional myocardial hypercontractility was suggested as a possible TTS-like syndrome model in animals [7]. Other possible mechanisms include coronary endothelial dysfunction, different cytokine activation, impaired fatty acid metabolism in cardiac tissue and multi-vessel spasm [8, 9].Treatment of TTS depends on patient clinical condition, and in most of the cases is supportive. In this retrospective study, we aimed to identify different features in the clinical presentation of patients with TTS as compared to those with ACS.

PATIENTS AND METHODS

Thirty-five consecutive patients who were hospitalized at the Galilee Medical Center from 2011 to 2015 with TTS were compared to 60 age- and sex-matched patients with ACS. The diagnosis of TTS was confirmed based on clinical presentation, finding of typical apical ballooning in echocardiography, absence of culprit coronary lesion in angiography, and demonstration of complete recovery of cardiac function and shape in repeat echocardiography. The ACS group included patients with ST and non-ST segment elevation acute myocardial infarction. A final diagnosis of acute myocardial infarction was confirmed after comprehensive workup including serial troponin levels, electrocardiogram (ECG), echocardiogram, and coronary angiography. Myocardial necrosis was based on rise and fall patterns of the hs-cTnI, with at least one value above the 99th percentile, using the fourth universal definition of myocardial infarction. The following data were collected: demographics, past medical history and atherosclerotic risk factors, preceding triggers, and features of the presenting symptoms. In addition, the following ECG changes were recorded: ST-elevation (at the J-point), ST-depression 80 msec following the J-point, and T-wave inversion at the nadir.

STATISTICAL ANALYSIS

Qualitative parameters were presented in average and standard deviation and were compared using Chi-square test and Fisher's exact test. Wilcoxon rank sum test and independent t-test were used to compare quantitative variables. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 19 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Patients with acute coronary syndrome were more likely to have coronary artery disease and atherosclerotic risk factors in the background. Interestingly, the prevalence of tobacco use, family history of coronary artery disease, and psychiatric disorders were similar between the groups. Table 1 summarizes the demographic and risk factors of patients with TTS and ACS. Most of the clinical features on admission (chest pain and the accompanied symptoms) were quite similar between the two groups as shown in Table 2. Of note, patients with TTS had higher heart rates (86 ± 17 vs. 79 ± 15, $P = 0.029$) and lower systolic blood pressure (129 ± 26 vs. 142 ± 30, $P = 0.034$). ECG changes were present in 86% and 83%, and were localized mainly in the anterior leads in 71% and 44% of the patients in the TTS and ACS groups ($P = 0.783$, $P = 0.033$, respectively). Cardiac catheterization in the ACS group revealed significant coronary artery disease in all patients, with demonstration of one vessel disease in 20%, two vessel disease in 34% and three vessel disease in 46%.

Table 1. Characteristics of the patients

Characteristic	Takotsubo syndrome (N=35)	Acute coronary syndrome (N=60)	*P* value
Age	67.6 ± 14.5	68.3±11.1	
Female	32 (91.4%)	55 (91.7%)	1
Hypertension	16 (45.7%)	47 (78.3%)	0.002
Hyperlipidemia	21 (60%)	49 (81.7)	0.029
DM	8 (22.9%)	38 (63.3)	< 0.001
Obesity	6 (17.1%)	27 (45%)	0.007
CAD	5 (14.3%)	23 (38.3%)	0.019
Family history of CAD	4 (11.4%)	13 (21.7%)	0.273
PAD	1 (2.9%)	16 (26.7%)	0.004
CKD	0 (0%)	17 (28.3%)	< 0.001
COPD	4 (11.4%)	11 (18.3%)	0.405
Tobacco use	8 (22.9%)	23(38.3%)	0.173
Psychiatric disorder	2 (5.7%)	3 (5%)	0.611
Preceding stressful event	21 (60%)	0 (0%)	< 0.001

CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, PAD = peripheral arterial disease

In the TTS group, coronary angiography was also performed on all patients. Results were significant for atherosclerotic artery disease in 10 (29%) patients, however, without evidence of a culprit lesion. The average left ventricular ejection fraction in the TTS group was 46 ± 5% on admission and a complete recovery (ejection fraction > 50%) was observed in 88% of the patients within 3–4 weeks. During angiography, left ventriculography was performed in 18 (51%) of the patients in the TTS group and demonstrated typical apical ballooning with basal hypercontractility. Average time of hospital stay was 4 days and 5 days in the TTS and ACS group, respectively ($P = 0.216$) with 45.7% and 50% of patients being admitted to the cardiac care unit, respectively ($P = 0.425$). During the hospitalization, peak creatinine levels were higher in the TTS group (1.9 vs. 0.8 mg/dl, $P = 0.004$). There were no mortality events in the two groups during the hospital stay and at 1-month follow-up.

DISCUSSION

Because most patients with TTS present with acute chest pain and more than 80% of them have elevated troponin and ECG changes, discrimination between TTS and ACS may be challenging [10]. TTS is common among postmenopausal females and is often preceded by an emotional or physical trigger. The diagnosis of TTS is mainly based on the clinical presentation,

Table 2. Clinical features and laboratory on admission and during hospitalization

Characteristic	Takotsubo syndrome	Acute coronary syndrome	P value
Chest pain	31 (88.6%)	54 (90%)	1.0
Dyspnea	18 (51.4%)	31 (51.7%)	1.0
Epigastric pain	6 (17.1%)	11 (18.3%)	1.0
Radiating pain	7 (20%)	24 (40%)	0.069
Syncope	4 (11.4%)	3 (5%)	0.417
Sweat	6 (17.1%)	22 (36.7%)	0.062
Heart rate (BPM) on admission	86 ± 17	79 ± 15	0.029
Systolic blood pressure on admission (mmHg)	129 ± 26	142 ± 30	0.034
Diastolic blood pressure on admission (mmHg)	76 ± 17	76 ± 15	0.922
Ejection fraction on admission	45%	54%	0.003
Peak troponin level (ng/ml)	4.0	27.7	< 0.0001
Peak CRP mg/l (0.2–5)	15.2	13.0	0.45
QT interval(msec)	468 ± 40	437 ± 33	< 0.001
Peak creatinine (mg/dl). (0.7–1.25)	0.8	1.9	0.004
Acute pulmonary congestion	5.2%	15%	0.004
In hospital mortality	0%	0%	

transient left ventricular dysfunction, ECG, biomarker levels, and the exclusion of a culprit coronary lesion.

In this retrospective study, we identified features to distinguish TTS from ACS based on clinical presentation and physical examination. As expected, most of the atherosclerotic risk factors were more common in the ACS group, except for tobacco use and family history of coronary artery disease [Table 1]. The features of the chest pain and its accompanied symptoms were similar in the two groups [Tables 2].

On admission, patients with TTS showed a significantly higher heart rate and lower systolic blood pressure compared to ACS patients. These differences can be explained by the fact that patients with ACS are more likely to have hypertension at baseline, and by the effect of the adrenergic surge that accompanies TTS. In addition, atrioventricular block that may be present in inferior wall myocardial infarction and causes bradycardia, is not supposed to be part of TTS. Although an emotional event is commonly reported to precede the onset of TTS, we did not find increased chronic psychiatric disorders such as depression or anxiety disorder among patients with TTS compared to those with ACS (5.7% vs. 5% respectively, $P = 0.611$). Cardiac troponin peak levels were significantly higher in the ACS group (27.7 ng/ml vs. 4.0 ng/ml, $P < 0.0001$). This finding is consistent with previous studies that demonstrated only slight elevation of troponin in TTS along with highly elevated natriuretic peptides [11]. ECG changes were predominant in the anterior leads in the majority of patients in the TTS group, although these changes are well documented in TTS and could not be reliable for diagnostic purpose. The lack of concordance between ECG changes and wall motion abnormality together with low troponin level may be suggestive for TTS. Peak CRP levels were similar in the groups. This result may be explained by the possible inflammatory mechanisms in the two conditions. QT segment was significantly longer in the TTS group, although no arrhythmic events occurred in this population.

All patients were initially treated as ACS with anti-platelet therapy, anti-coagulation, and statins until final diagnosis was confirmed. Patients were managed according to the current guidelines and local policy by trained physicians in cardiology and acute cardiac care. The decision whether to admit a patient in the cardiology or cardiac care unit was based on the hemodynamic condition on presentation. In our study, the length of stay was similar between TTS and ACS patients (4 days vs. 5 days, respectively $P = 0.216$).Peak creatinine level was higher in the TTS group (1.9 vs. 0.8 mg/dl, $P = 0.004$). Acute kidney injury in the ACS group may be explained by higher events of contrast-induced nephropathy (due to larger amounts of contrast media during therapeutic procedure) and by the use of nephrotoxic agents commonly used in heart failure. No patients needed dialysis during the hospitalization.

Acute congestion was more prominent in the ACS group (15% vs. 5.2%, $P = 0.005$) indicating more dramatic clinical course in ischemic patients. Primary ventricular fibrillation treated by DC shock occurred in two patients in the ACS group and was not documented in the TTS group. There was no need for circulatory or respiratory support (other than noninvasive supplementary oxygen) and no mortality events in the two groups during the hospital stay and in 1-month follow-up. Complete cardiac recovery (ejection fraction > 50%) was observed in 88% of the patients within 3 to 4 weeks. Re-hospitalization in one month was documented in 0.08% in the TTS group and in 0.03% in the ACS group ($P = 0.38$).

In general, the majority of the patients with TTS demonstrated a benign course with complete normalization of the cardiac function, and therefore should be managed conservatively. Hemodynamically stable low-risk patients with preserved or mildly reduced systolic left ventricular ejection fraction without significant secondary mitral regurgitation may benefit from beta-blockers and ACE inhibitors for reverse remodeling. The contemporary echo techniques such as speckle-tracking strain imaging used in recent onset cardiomyopathy [12] may also be implemented in TTS. In patients with acute decompensat-

ed heart failure and those with high-risk features such as low blood pressure and hypoperfusion on admission, beta-blocker therapy with short acting alpha-blockers and avoidance of sympathomimetic drugs are recommended, with continuous hemodynamic monitoring. Mechanical support using extracorporeal membrane oxygenation (ECMO) may be needed in severely ill patients [13].

We highlight the significance of multimodality approach in patients with suspected of TTS using biomarker levels, echocardiography, and angiography, as clinical judgment and ECG are not sufficient to discriminate this syndrome from other diseases due to the lack of unique clinical feature and the relatively weak association with psychological triggers.

LIMITATIONS

The study has two main limitations. This retrospective study included a small sample size; however, the results reflect the data regarding patients with relatively low incidence disease through 5 years. It is important to investigate the behavior of this cardio-psychologic syndrome in our country, regardless of the existing data in the literature.

Natriuretic peptide (NP) levels were not available for the patients due to the lack of the assays during the study years. NP levels are used as marker in TTS as most patients demonstrate high NP levels with relatively low troponin level.

CONCLUSIONS

We could not identify a reliable clinical feature that may be used to distinguish TTS from ACS on admission. Even though a mental or physical trigger is traditionally thought to precede TTS, it is reported in only 60% of the patients, and the absence of such trigger does not exclude TTS. TTS should always be in the differential diagnosis in women presenting with chest pain.

Correspondence

Dr. G. Moady
Dept. of Cardiology, Galilee Medical Center, Nahariya 22100, Israel
Fax: (972-4) 910-7279
email: gassan_muady1@hotmail.com

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Capsule

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

Transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD) are severe monogenic diseases with severe and potentially life-threatening manifestations. BCL11A is a transcription factor that represses γ-globin expression and fetal hemoglobin in erythroid cells. **Frangoul** and colleagues performed electroporation of CD34+ hematopoietic stem and progenitor cells obtained from healthy donors, with CRISPR-Cas9 targeting the *BCL11A* erythroid-specific enhancer. Approximately 80% of the alleles at this locus were modified, with no evidence of off-target editing. After undergoing myeloablation, two patients - one with TDT and the other with SCD-received autologous CD34+ cells edited with CRISPR-Cas9 targeting the same *BCL11A* enhancer. More than a year later, both patients had high levels of allelic editing in bone marrow and blood, increases in fetal hemoglobin that were distributed pancellularly, transfusion independence, and (in the patient with SCD) elimination of vaso-occlusive episodes.

N Engl J Med 2021; 384:252
Eitan Israeli