THE TAKO-TSUBO CARDIOMYOPATHY OR BROKEN HEART SYNDROME. CLINICAL CHARACTERISTICS, DEMOGRAPHICS AND PROGNOSIS OF THIS ENTITY IN ALSACE, FRANCE

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REZUMAT

Autorii japonezi au descris o nouă entitate clinică, ce asociază akinezie apicală şi hiperkinezie bazală cardiacă, în absenţa unei coronaropatii, pe care au numit-o cardiomiopatia Tako-Tsubo. Acest sindrom este caracterizat printr-o gravă, dar rapid reversibilă disfuncţie sistolică ventriculară stângă, declanşată de stres psihologic acut şi observat de obicei intr-o vârstă. Prezentarea clinică de debut este asemănătoare unui sindrom coronarian acut. Analiza unei cohorte din Alsacia prezintă profilul clinic al acestei cardiomiopatii. Timp de 24 luni, 30 de pacienţi (27 femei la menopauză şi 3 bărbaţi, cu vârsta cuprinsă între 41 şi 87 ani, în medie 64 ± 23 ani) au fost recrutaţi din zona Alsaciei. Durerea toracică a fost precedată de un eveniment deosebit de stresant la toţi pacienţii. Nivelul catecolaminelor plasmatice nu a fost corelat cu disfuncţia ventriculară stângă. Mai mult, nu au putut fi dovedite corelaţii între nivelle de troponina, CPK, supradenivelarea segmentului ST şi FEVS (fracţia de ejeceţie ventriculară stângă). 28 de pacienţi (93,3%) au prezentat o rapidă ameliorare a FEVG după 3 săptămâni (cu o creştere medie 23 ± 18% faţă de valoarea anterioară), un mic proporţie (6,7%) au prezentat afecţiuni hemodinamice ce a necesitat agenti vasopresori. Prognosticul a fost bun, toţi pacienţii au supravieţuit, în ciuda insuficienţei cardiace severe. După explorări complete cardiovasculare, 21 pacienţi au fost diagnosticaţi cu cardiomiopatia Tako-Tsubo.

Cuvinte cheie: cardiomiopatia Tako-tsubo, disfuncţie sistolică ventriculară stângă, femei la menopauză

ABSTRACT

Japanese authors have described a new clinical entity associating apical akinesias and basal hyperkinesias without significant coronary artery disease under the name of the Tako-Tsubo cardiomyopathy. This syndrome is characterized by acute but rapidly reversible left ventricular systolic dysfunction triggered by psychological stress, usually observed in elderly women. The clinical onset is usually that of an acute coronary syndrome. The patient cohort from the Alsace that demonstrates the clinical profile of this cardiomyopathy is presented. Over a 24-month period, 30 patients were recruited within a community - based practice in the Alsace area. Twenty seven patients were post menopausal women and 3 patients were men, aged 41 to 87 years (mean 64 ± 23 years). Each patient experienced particularly stressful events immediately preceding onset of chest pain. Catecholamine levels did not correlate with the marked left ventricular dysfunction. Furthermore, no correlations between troponin Ic, CPK levels, ST segment elevation and LVEF (left ventricular ejection fraction) could be evidenced. In 28 patients (93.3%) rapid restoration of LVEF to previous values occurred after 3 weeks (mean increase was 23 ± 18%). A small proportion of patients (6.7%) remained hemodynamically compromised and required vasopressor agents. Prognosis was good, provided the patients survived the severe heart failure. After complete cardiovascular explorations and follow-up we concluded that 21 patients presented Tako-Tsubo cardiomyopathy.

Key Words: Tako-Tsubo cardiomyopathy, left ventricular systolic dysfunction, post menopausal women

INTRODUCTION

Tako-Tsubo cardiomyopathy or transient left ventricular apical ballooning syndrome remains poorly understood. Several hypotheses have been raised, including multivessel epicardial infarction, myocardial dysfunction mediated through catecholamine-induced damage, microvascular coronary spasm or dysfunction, neurogenically mediated myocardial stunning and focal myocarditis.¹⁴
Acute and rapidly reversible left ventricular (LV) dysfunction can be triggered by profound psychological stress in a recently recognized scenario. Chest pain and worsening of dyspnea were common admission causes in a study published by Kurisu et al. Electrocardiograms showed T-wave inversions in precordial leads and acute coronary syndrome was suspected. Left ventricular apical ballooning was observed by echocardiogram and left ventriculography. Coronary arteriography did not reveal any significant stenosis. Left ventricular motion normalized at one month follow-up and there were no increases in specific markers for myocardial damage, such as myocardial band fraction of creatine kinase and troponin.

Prior reports have largely been confined to Japanese patients, which raised the possibility of geographically restricted cardiovascular syndrome. Therefore, it is timely to report a patient cohort from the Alsace that demonstrates the clinical profile of this cardiomyopathy in a European population.

MATERIAL AND METHODS

Patient Population
Over a 24-months period, 30 patients referred to two public hospitals (CHU Hautepierre, Strasbourg and CHG Haguenau, France) were enrolled in this observational study. Mayo criteria for the clinical diagnosis of transient left ventricular apical ballooning syndrome or Tako-Tsubo cardiomyopathy were met in all patients:

1. Acute substernal chest pain with ST-segment elevation and/or T-wave inversion;
2. Absence of significant coronary arterial narrowing by angiography;
3. Systolic dysfunction (ejection fraction 34±14%), with abnormal wall motion characterized by akinesia/hypokinesia of the mid-to-distal portion of the LV chamber, with hypercontractile basal LV, i.e., “apical ballooning”;
4. Profound psychological stress (e.g., death of relative, domestic abuse, arguments, catastrophic medical diagnoses, devastating financial or gambling losses) in preceding days, triggering the cardiac events.

None of the patients was taking cardioactive medications before admission or using vasoconstrictor substances such as cocaine or triptans. The patients presenting hypertrophic cardiomyopathy or obstructive epicardial coronary artery disease, recent significant head trauma, intracranial bleeding, pheochromocytoma, or a history of Raynaud’s syndrome, were excluded from our study.

The study complied with the Declaration of Helsinki and was approved by our institutional Ethics Committee.

Clinical Assessment
The patients were assessed by history and physical examination, 12-lead ECG, serum troponin, coronary arteriography and ventriculography, echocardiography, cardiac MRI or myocardial scintigraphy done after admission.

Troponin I, creatine kinase (CK), CK-MB were measured upon admission and subsequently every 6 hours until recovery of normal values, in blood samples obtained from an antecubital vein into gel-filled tubes. Measurements of Troponin Ic, CK, CK-MB, CRP, leukocyte level, Hb, HbA1c, creatinine level, lipid levels were performed following standard procedures. Serum concentrations of brain natriuretic peptide (BNP) were measured by enzyme immunoassay. Plasma levels of catecholamines were measured on hospital day one and after three weeks with high performance liquid chromatography in six patients (20%). According to standard procedures for sampling of catecholamines, patients remained supine for at least 60 minutes before undergoing phlebotomy. Blood samples were placed on ice and immediately centrifuged and the plasma was frozen.

Echocardiography studies were performed in a standard fashion, from the apical two and four chamber view; LVFE was calculated using the Simpson method. All examinations were performed using GE-VIVID-7 ultrasound equipment with a 2.5 MHz transducer.

Coronary angiography and contrast LV were performed upon admission in all patients with a 4 or 6 French catheter using the Seldinger technique with all standard projections. CAD was defined as > 50% reduction in lumen diameter. LV was investigated in the 30° right anterior oblique projection. LV ejection fraction was calculated by mean of the area-length method using quantitative LV analysis. We also performed the coronary spasm provocation test by intracoronary infusion of Methergin in four patients during the acute phase (50μg in the right coronary artery and 100μg in the left coronary artery). We defined coronary spasm as a reduction in diameter of >75% compared with the diameter before intracoronary infusion of Methergin.

201Thallium or 99Technetium myocardial scintigraphy were performed in the first three weeks in six patients. Briefly, after overnight fasting, an intravenous bolus injection of 201Tl was given at rest,
and data acquisition was started within 20 minutes after radionuclide injection using a three-headed SPECT system. A total of 60 projection images were obtained in 128x128 matrixes over 360°, with 30s per view. After reduction of the matrix size of the projection data to 64x64, tomography images along the vertical long and short axes were created. The Spect image of the LV was divided into 17 segments for semi-quantitative analysis.

MRI studies were obtained within the first 3 weeks or in the chronic phase after admission. In each of the investigated patients, abnormalities were assigned to coronary arterial vascular territories, according to previously established criteria. MRI was performed with a Siemens Sonata 1.5-T scanner. Standard TrueFISP (fast imaging with steady-state precession; TI = 240 to 300 ms) cineimages were acquired in 3 long-axis slices and 11 to 15 short-axis slices, 7 mm in thickness with a 3 mm interslice gap, achieving full ventricular coverage. A delayed enhancement protocol was used 10 to 20 minutes after intravenous administration of gadolinium-DTPA (0.2 mmol/kg) with breath-hold inversion-recovery turboFLASH (fast low-angle shot) or segmental TrueFISP sequences. Regional wall-motion abnormalities (e.g., hypokinesia, akinesia or dyskinesia) were assessed in the 17-segment model of the LV chamber.

Statistical analysis

Data were expressed as means ± SD. Epi Info v. 3.4 and SPSS v. 10 software were used for the statistical analysis. Significance was considered for p < 0.05.

RESULTS

Demographics and Clinical Presentation (Table 1)

Table 1. Baseline characteristics of the study group.

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
<th>Number of patients (n=30)</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>27 F</td>
<td>90%</td>
</tr>
<tr>
<td>Stress</td>
<td>26</td>
<td>86.7%</td>
</tr>
<tr>
<td>HTA</td>
<td>23</td>
<td>76.7%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>15</td>
<td>50%</td>
</tr>
<tr>
<td>Heredity</td>
<td>4</td>
<td>13.3%</td>
</tr>
<tr>
<td>Body weight</td>
<td>4</td>
<td>13.3%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
<td>16.7%</td>
</tr>
<tr>
<td>Smoking</td>
<td>7</td>
<td>23%</td>
</tr>
</tbody>
</table>

Characteristics of patients and possible triggering factors

Proportion of patients: 27 were female (90%) and 3 were men (10%), 41 to 87 years old (mean 64 ± 23 years), 90% were ≥ 50 years, and all were Caucasian. After complete explorations, 21 patients were considered having the Tako-tsubo cardiomyopathy syndrome. The vast majority of patients with Tako-tsubo cardiomyopathy was women (95.23%). The duration of hospital stay was 15.26±8.87 days.

The vast majority of patients (90%) had initial clinical findings consistent with acute coronary syndrome, including ST-segment elevation myocardial infarction, recent abrupt onset of severe substernal chest pain (70%), and/or heart failure (50%). No patient had clinical evidence of volume overload with pulmonary congestion or peripheral edema. Relevant history included smoking (23.3%), hypercholesterolemia (50%), hypertension (76.7%), obstructive lung disease heredity (13.3%) or diabetes (16.7%). Body weight was normal in 86.7% of the patients. Preceding significant emotional stress could be identified in 86.7% patients.

Electrocardiography findings

Initial ECGs showed ST-segment elevation of 2 mm in two contiguous leads in 12 patients, usually in DI, aVL, and precordial leads, associated with T-wave inversion in the same lead; T-wave inversion without ST elevation became more predominant and diffuse with time, mostly in the anterior (n = 11) but also in lateral (n = 10) and inferior (n = 2) leads. Other abnormalities were QS (or Q) waves, usually in V1 toV3, (n = 7), low (< 0.5 mV) limb-lead voltages (n = 9), and corrected QT interval (QTc) > 450ms (n = 6). (Fig. 1)

ST-segment elevation resolved by hospital discharge in all 12 patients, but QS (Q) waves did not change. Atrial fibrillation was present to 13.3% patients, and another 30% of the patients presented conduction abnormalities (atrioventricular or bundle branch block) not requiring implantation of a pacemaker.

Laboratory tests

Initial serum troponin was normal in one patient (cTnI <0.07 ng/ml) and definitely abnormal in 90%. In the patients with normal troponin levels on admission, peak levels became abnormal by 24 hours. Mean peak Troponin Ic levels were 7.04 ± 6.72 ng/ml and CPK levels were 393.43 ± 42.27 U/ml. Abnormal elevated BNP levels > 400 ng/l were found at admission in 53.3% patients.
Renal failure was present in 40% of patients (creatinine clearance <60 ml/min). Anemia was present in 23.3% of patients and hypokalemia (K<3.5 mmol/l) in 16.7%. HbA1c > 6% was present in 20% of patients. Total cholesterol values >2 g/l were observed in 40% of the patients, LDL>1 g/l in 40% and HDL<0.50 g/l in 26.7%. Inflammatory status with elevated levels of CRP >4 mg/l and peak leukocytes > 10000/mm³ were observed in 53.3% patients. The inflammatory status did not correlate with Troponin Ic and CPK levels, but correlate with the dyslipidemia. (Fig. 2)

Myocardial scintigraphy
Myocardial perfusion was performed at inclusion in just 20% of the patients and at a 3 month follow-up for 20% of these patients. Thallium-201 scintigraphy revealed a defect confined to the apical region that disappeared with convalescence and normalization of the left ventricular wall motion. (Fig. 4)

In addition, myocardial fatty acid metabolism measured using iodine-123-beta-methyl-p-iodophenyl penta-decanoic acid (123I-BMIPP) was more severely impaired than myocardial perfusion and a discrepancy in the sympathetic innervations between the apical and
basal region was seen. Myocardial perfusion at rest with $^{123}$I-BMIPP is the essential examination that must be used for differential diagnosis between Tako-Tsubo cardiomyopathy and acute coronary syndrome.

**Myocardial resonance imaging**

MRI was performed during the acute phase and at hospital discharge in eight patients (26.7%), identified with systolic dysfunction. Diffuse segmental wall-motion abnormalities that encompassed LV myocardium in multiple coronary arterial vascular territories, with the characteristic apical ballooning was observed in four patients; other four had abnormal regional wall motion. Delayed gadolinium hyperenhancement was not present in six of eight patients, consistent with viable myocardium and the absence of myocardial scar and infarction. Two patients who presented with cardiac arrest, showed hyperenhancement confined to the LV apex, representing a small myocardial infarction. (Fig. 5)

In 20% of the cases, MRI was performed during the chronic phase after three weeks. One patient presented abnormal regional wall motion involving areas of the LV beyond the vascular distribution of a single coronary artery.

After explorations, 21 patients were considered having the Tako-Tsubo cardiomyopathy syndrome, three with microvascular spasm, and four with myocardial infarction followed by reperfusion, one with focal myocarditis and one with pulmonary embolism.

**MANAGEMENT**

After discharge patients were maintained on medications including ACE inhibitors or ARAII angiotensin receptor blockers (n = 18), β-blockers (n = 20), diuretics (n = 16), calcium antagonists (n = 5) and magnesium (n = 1). Seventeen patients were taking statins, aspirin or both after hospital discharge. Vasopressor agents (dobutamine) were administered in two patients with marked hypotension to sustain cardiac output and systemic blood pressure and they did not require mechanical and hemodynamic support with intra-aortic balloon counter pulsation. GP-IIb/IIIa antagonists were used in two patients, because of the clinical misperception of an evolving ST-segment infarction.

**DISCUSSIONS**

The transient LV apical ballooning syndrome is a new diagnostic entity with typical characteristics. Each patient experienced particularly stressful incidents immediately preceding the onset of symptoms. For all, these were acute psychological triggers, such as the unexpected death of a close relative, confrontations and arguments with friends or relatives, or emotionally charged counseling sessions, devastating financial situations, etc. Emotional or physical stress might play a key role in Tako-Tsubo cardiomyopathy.

Because the onset of this syndrome is often preceded by emotional or physical stress, catecholamine-mediated multivessel epicardial spasm, micro vascular coronary spasm, or possible direct catecholamine-mediated myocyte injury have been advocated as possible pathophysiological mechanisms. However, the evidence supporting any of these possible mechanisms is not compelling.

The ergonovine test shows the coronary spasm in 10% of patients, although this mechanism is considered insufficient to reveal the entire affected territory of the left ventricle. Vasospastic ischemia
is much more common in Japan than the rest of the world.2,7,11,14

Plasma catecholamines were slightly elevated. Catecholamine levels did not correlate with the marked left ventricular dysfunction and did not correlate with the severity of heart failure or BNP. However, in the absence of prospective data evaluating plasma catecholamine levels prior to the development of clinical abnormalities, a causal relationship cannot be proven and the elevated catecholamine levels may be an epiphenomenon or a consequence of the hemodynamic abnormalities associated with this syndrome.1,4,10,12,15

Myocarditis has been proposed as possible alternative mechanism. However, studies that have used endomyocardial biopsy and viral serology do not support this hypothesis.10,12 In these studies, the inflammatory status did not correlate with troponin Ic and CPK levels, and with the cardiovascular risk factors, different from acute coronary syndrome. Furthermore, BNP was considered a mortality predictor for heart failure.

The BNP correlated with the inflammatory syndrome, but not with troponin and CPK levels. The BNP was correlated with the NYHA class and LVEF upon admission, but not with prognosis. Prognosis was good, compared to myocardial infarction, taking into consideration that the patients survived the severe heart failure state.5,6,9,10,13,16,17

ST-segment elevation did not correlate with Troponin Ic and CPK levels in previous studies. Catecholamine cardiomyopathy or a high plasma level of norepinephrine can cause ST-segment and regional ventricular wall motion abnormalities.1,9-12,18-20 T-wave inversion (without ST elevation) became more predominant and diffuses with time, mostly in the anterior. This modification was not correlated with hypokalemia or anemia in several studies.1,4,7,14,15

Coronary angiography is completely normal in most patients and shows mild, non-obstructive coronary lesions (<50% luminal diameter stenosis). Ventriculography correlated with echocardiography and MRI, but did not correlate with troponin C and CPK levels. Myocardial scintigraphy or MRI identified diffusely distributed segmental wall-motion abnormalities that encompassed LV myocardium in multiple coronary arterial vascular territories, correlated with echocardiographic findings.1,2,4,5,8,12,15,19,21,24

MRI showed hyperenhancement confined to the LV apex, beyond the vascular distribution of a single coronary artery. MRI evidenced also necrosis, focal myocarditis and reperfused myocardial infarction.5,12,13

The patients were treated according to established guidelines for ST-elevation myocardial infarction or acute coronary syndrome, with combinations of β-blockers, aspirin, nitrates, statins and heparin. The GP IIbIIIa inhibitors and thrombolysis are forbidden in this entity, being considered a medical error. In the absence of studies specifically evaluating different therapeutic, the treatment of this syndrome should be addressed to an idiopathic cardiomyopathy.16,17

Complete resolution of the apical wall motion abnormality and of initially depressed LVEF ensure a favorable evolution.2,9-12,21,25-27

Mid-ventricular wall-motion abnormalities, apical akinesia or dyskinesia with preserved or hyperkinetic contractile function of the basal LV segments, are characteristic. Local release of catecholamines from cardiac sympathetic afferent neurons seems to be an unlikely explanation because of the higher norepinephrine content and greater density of sympathetic nerves at the base of the heart when compared with the apex.

However, several case reports of patients with pheochromocytoma-related cardiomyopathy described a similar distribution of LV wall-motion abnormalities. Furthermore, there is some evidence suggesting that the apical myocardium may be more responsive to sympathetic stimulation and may be more vulnerable to sudden catecholamine surges. A longitudinal, base-to-apex decline in LV myocardial perfusion, as described in patients with coronary risk factors, was also proposed as a possible alternative explanation.28,29,30-32

The vast majority of patient’s with Tako-Tsubo cardiomyopathy were females (95.2%). Several explanations have been proposed. Thus, sex hormones may exert important influences on the sympathetic neurohormonal axis and vasoreactivity. Women also appear to be more vulnerable to sympathetically mediated myocardial stunning, and post-menopausal alteration of endothelial function in response to reduced estrogens levels has been advocated as a possible alternative explanation.8,21,25-33

LIMITATIONS

Our observational study has several limitations. Considering the rareness of this disease, the study was conducted on a small cohort. We did not carry out the catecholamine assessment in all patients. The imagery was partially performed; every patient had an angiography and an echocardiography, but only several had the MRI and myocardial scintigraphy.
CONCLUSIONS

The Tako-Tsubo syndrome:
1. Is a reversible cardiomyopathy triggered by psychologically stressful events.
2. Occurs in older women and may mimic evolving acute myocardial infarction or coronary syndrome.
3. Must be taken into consideration regardless the geographical area.
4. The complete explorations (echocardiography, angiography, MRI and myocardial scintigraphy) contribute to a better and more complete diagnosis and are important for evolution, consequences and appropriate medical therapy.

REFERENCES