Case Report

Takotsubo Syndrome and its Relationship with Major Depressive Disorder: Case Report

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Introduction

Takotsubo syndrome (TTS) is a medical condition characterized by reversible regional dysfunction of the left ventricle (LV) and/or right ventricle. TTS is often triggered by situations of acute physical or emotional stress. It presents characteristics similar to an acute coronary syndrome (ACS) event, but without coronary abnormality evidenced by exams such as angiography.[1] Furthermore, upon admission, patients with TTS also manifest substantially lower left ventricular ejection fraction (LVEF) values, when compared to those with ACS. Nonetheless, even with these lower levels, the chances of cardiovascular damage are lower, and the restoration of LVEF is more satisfactory.[2]

Although the pathophysiology of TTS is complex and, in part, unknown, studies suggest that exacerbated sympathetic activation, confirmed by increased levels of plasma catecholamines, and adrenergic drugs may precipitate the condition. It predominantly occurs in postmenopausal women. However, it can affect younger women and men, and it is estimated that 1% to 3% of all patients and 5% to 6% of female patients who undergo coronary angiography due to suspected ACS have TTS.[3] Reproductive and hormonal factors and stressful emotional events are associated with greater occurrence of TTS in women,[2] whereas the physical factor is the most frequent agent in men, as well as in patients undergoing chemotherapy treatment.[2]

Regarding its etiopathogenesis, several emotional (divorce, death of a family member, and financial problems) or physical (physical activity, thyrotoxicosis, sepsis, pregnancy, ACS, and stroke) stressors have been described as possible triggers of TTS.[4] The sympathetic stimulation that is triggered can lead to direct toxicity in cardiomyocytes, epicardial or microvascular coronary artery spasm, and acute coronary microvascular dysfunction.[5] Despite this established causal relationship, some individuals do not present acute stress factors, which suggests the existence of predisposing substrates that still need to be grasped. In this sense, the influence of psychiatric disorders as a predisposing psychopathological substrate in patients with TTS has been the subject of investigation.[6]

Even though it is a rare, reversible condition with benign sequelae, TTS can present events such as acute heart failure and pulmonary edema, with a mortality rate of approximately 5%.[7] Due to the fact that its clinical manifestations, including acute chest pain, dyspnea, elevated myocardial necrosis markers, and electrocardiographic changes, are analogous to those found in ACS, TTS is still underdiagnosed and neglected.[8,9]

The objective of this case report was to promote better understanding of TTS in the context of patients with psychiatric disorders and provide information that could impact the clinical practice of general practitioners.

Case Report

We report the case of a 76-year-old female patient who sought care, reporting severe chest pain, associated with an episode of vomiting and profuse sweating that lasted 1 hour and spontaneously resolved. She stated that the previous day, she had the same pain, but with less intensity. The pain lasted approximately 1 hour, was retrosternal without irradiation, without associated symptoms, and it spontaneously resolved. She reported that the condition began when she was nervous regarding a family discussion.

She underwent an electrocardiogram, which showed an inactive electrical zone in the anteroseptal wall. Ultrasensitive troponin level was 1616 ng/L. The transthoracic echocardiogram revealed LVEF of 35%, with the following LV wall motion abnormalities: middle anterior wall hypokinesia and akinesia of the middle anterior septum, the middle inferior septum, and the entire apex. She was referred to the hemodynamics laboratory, where catheterization was performed, revealing coronary arteries with no evidence of significant obstructive lesions, and LV wall motion abnormalities suggestive of adrenergic cardiomyopathy (takotsubo). After 15 days, she underwent magnetic resonance imaging, which showed preserved systolic performance, hypokinesia of the middle and apical segments of the LV, and mild late enhancement areas with a non-ischemic pattern and diffuse distribution suggestive of myocardial necrosis and septal thickening. These findings were compatible with TTS. Without recurrence of chest pain, she was treated with a beta-blocker, antihypertensives, and statins, and she was discharged, with full coagulation for 3 months. She returned for follow-

Keywords

Takotsubo Cardiomyopathy; Depression; Mental Disorders

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Manuscript received February 02, 2024, revised manuscript May 20, 2024, accepted June 16, 2024
Editor responsible for the review: Luis Beck-da-Silva

DOI: https://doi.org/10.36660/abchf.20240003i

up in 3 months, and the new transthoracic echocardiogram revealed complete resolution of the condition as follows: left atrium: 34, septum 43, LVEF 72%, mild left atrial dilation, preserved LV end-systolic diameter, and normal LV wall motion (Table 1). The anticoagulant was discontinued, but beta-blocker use was continued.

The patient was undergoing outpatient cardiology care at this service due to a positive Chagas test, with no evidence of Chagas cardiomyopathy. She had dyslipidemia, uncontrolled systemic arterial hypertension, and chronic obstructive pulmonary disease (GOLD 1). She had a history of tobacco and alcohol use, as well as prior history of glaucoma and stroke 6 years ago, without sequelae. The patient had long-standing major depressive disorder (MDD) and used clonazepam, fluoxetine, and nortriptyline hydrochloride for 3 years, when these medications were stopped and bupropion was prescribed. After 1 year, bupropion was discontinued and amitriptyline hydrochloride was prescribed, which she used irregularly for 7 years. She discontinued use of her own accord, having been off the medication for 2 years before the TTS occurred.

Table 1 – Left ventricular ejection fraction and wall motion on electrocardiography

	2015 (before TTS)	2022 (during TTS)	2022 (after TTS)	2023 (follow-up)
LVEF	63%	35%	72%	62%
LV wall motion	No segmental abnormalities	Middle anterior wall hypokinesia; septal akinesia	No segmental abnormalities	No segmental abnormalities

LV: left ventricle; LVEF: left ventricular ejection fraction; TTS: takotsubo syndrome.

Discussion

Even though it is a benign condition, the etiopathogenesis of TTS is still a subject of investigation. Recent research has investigated the susceptibility of patients with psychiatric disorders to developing TTS. Anxiety and depression are often associated, especially in cardiocirculatory disorders. Sancassiani et al.,[10] in a 2018 case-control study, found a significant association between TTS with depressive disorders and the use of antidepressants; however, they did not confirm an association with anxiety disorders.

A case-control study of risk and mortality markers provided evidence that, although physical factors play a prominent role as triggers, the majority of people affected by TTS had associated psychiatric or neurological conditions.[11]

The 2022 study carried out by Pozzi et al.[6] compared patients who presented TTS and ACS, with similar cardiovascular risk factors, undergoing comprehensive lifetime psychiatric assessment. The TTS group had a higher prevalence of mood disorders, including MDD, bipolar disorder, dysthymia, and anxiety disorders such as generalized anxiety disorder, panic disorder, and agoraphobia, when compared to the SCA group. Patients with TTS also had a significant tendency to use psychotropic medications, have substance abuse issues, and consult with a psychologist or psychiatrist.

Based on this evidence, the hypothesis was proposed that heart-brain interaction plays a fundamental role in the development of TTS. Structural anatomical brain differences between patients with TTS and healthy controls were analyzed.[12] Among the main differences found, hypoconnectivity of central brain regions associated with autonomic functions and regulation of the limbic system, such as the amygdala, stood out in patients with TTS, suggesting autonomic-limbic integration in its pathophysiology.[12]

The amygdala is a component of the limbic system that plays a fundamental role in the response to acute stressors, and its activity independently predicts cardiovascular events.[13] Corroborating these findings, 18F-FDG-PET/CT images have demonstrated that the basal activity of the amygdala is greater in individuals who subsequently develop TTS, supporting the existence of a predisposing neurobiological substrate in its genesis.[14] Psychological stress can act on the cardiovascular response, through neuroendocrine pathways, such as the adrenal medulla (producing catecholamines through sympathetic stimulation), the hypothalamic-pituitary-adrenal axis, and reduced vagal tone.[15]

Patients with TTS have significantly more psychological changes compared to those reported with ACS, showing the importance of considering psychological dimensions in the context of the pathology. The prevalence of depression in patients with TTS can range from 20.5% to 48%; this means that perhaps half of patients may experience depressive symptoms.[16] These depressive symptoms are often exacerbated by hyperactivity of the hypothalamic-pituitary-adrenal axis and, consequently, by increasing cortisol levels.[17]

Diverse psychotherapeutic and psychopharmacological approaches are available to assist patients in managing stress and depression, including resources such as self-help books, counseling services, cognitive-behavioral and group therapy, relaxation techniques, and the use of psychotropic medications. The effectiveness of psychotropic medications in preventing and treating TTS symptoms is a subject of debate, with diverging opinions.[17] While some authors question their usefulness, others believe them to be an essential tool.

According to several studies, beta-blockers may be used to control anxiety, especially in postmenopausal women. In some cases, they may be prescribed for prolonged periods to control the production of stress-related hormones. On the other hand, the main objective of treatment with antidepressants is to relieve symptoms of depression and anxiety, in order to prevent the development of TTS.[18]

MDD is associated with an increase in the density of postsynaptic beta-adrenergic receptors. Long-term antidepressant treatment regulates beta-1 adrenergic receptor levels, decreasing their density by means of several

strategies. Even with this reduction, a paradoxical increase in intracellular cAMP levels is observed, demonstrating that the activation of the cAMP system is crucial to antidepressants' therapeutic action. The CREB transcription factor is an important target of these treatments, and the *BDNF* gene is regulated by CREB. Severe stress is associated with decreased *BDNF* expression in the hippocampus. A current theory suggests that long-term antidepressant treatment increases the expression of *BDNF* and its TrkB receptor, due to the intensified activity of the serotonergic and noradrenergic systems.[17]

Myocardial stunning in TTS represents a catecholamine-induced cardiomyopathy, resulting from high concentrations of plasma adrenaline. Some antidepressant classes can act to regulate catecholamine levels; therefore, it is plausible to infer that there is a possible relationship between the interruption of the treatment by the patient under analysis and the triggering of TTS.[19]

Overall, the results of this study are concluded to reveal the importance of comprehensive care that includes management of cardiac conditions and mental health in patients with TTS; therefore, it may be fundamental to address depression and other mental health issues in order to improve these patients' quality of life and prognosis. In essence, treating the underlying mental illness may help reduce the risk of cardiac complications related to high levels of catecholamines; however, there is still no definitive scientific evidence showing that the use of common antidepressants would have an impact on the genesis and progression of TTS.

Author Contributions

Conception and design of the research: Silva WJ, Faldoni FLM; Acquisition of data: Silva WJ, Sembeneli G, Bueno PPA, Rodrigues RC, Gil FM; Writing of the manuscript: Silva WJ, Sembeneli G, Bueno PPA, Rodrigues RC, Gil FM, Faldoni FLM; Critical revision of the manuscript for content: Faldoni FLM, Domingos CHC.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade de Ribeirão Preto under the protocol number CAAE 09815219300005498. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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