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Review Article

Takotsubo syndrome

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ABSTRACT

Takotsubo syndrome is a reversible acute heart failure frequently precipitated by an emotional or physical stress. The clinical presentation resembles acute coronary syndrome. Pathogenesis is complex and may involve brain-heart axis and neuro-hormonal stunning of the myocardium. Coronary angiography reveals normal epicardial arteries with no obstruction or spasm. NT-ProBNP maybe remarkably elevated. Regional wall motion akinesia (RWMA) of left ventricle extends beyond the territory of one coronary artery. Reduced left ventricle ejection fraction (LVEF) and RWMA recover in 6–12 weeks. Prognosis is generally good. Recent meta-analysis shows in-hospital mortality of 1–4.5% and recurrence rate of 5–10% during five year follow-up.

Contents

Abbreviations: ACS, acute coronary syndrome; ECG, electrocardiography; ECHO, echocardiography; EF, ejection fraction; ECMO, extra-corporeal membrane oxygenator; HPA, hypothalamus pituitary axis; IABP, intra-aortic balloon pump; LVAD, Left ventricle assist device; LMWH, Low molecular weight heparin; LVOT, left ventricle outflow tract; LV, left Ventricle; MR, mitral regurgitation; MRI, magnetic resonance imaging; NIS, Nationwide Inpatient Sample; NSTEMI, Non-ST elevation myocardial infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; RWMA, regional wall motion abnormality; SAM, systolic anterior motion; STEMI, ST elevation myocardial infarction; SAH, subarachnoid haemorrhage; TS, Takotsubo syndrome.

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1. Introduction

Takotsubo syndrome (TS) is an acute reversible heart failure characterized by transient wall motion abnormality of left ventricle (LV) usually following a stressful event.[1] Clinically it mimics acute coronary syndrome (ACS) and presents with chest pain, dyspnoea and hypotensive shock. Electrocardiography (ECG) reveals ST segment elevation or depression, T wave inversion and prolonged QTc interval. There is elevation of cardiac biomarkers like troponin and pro-brain natriuretic peptide (pro-BNP). Transthoracic two-dimensional echocardiography (2D-ECHO) shows regional wall motion abnormality (RWMA), not restricted to one coronary artery territory. Left ventricle ejection fraction (LVEF) is decreased. Coronary angiography, however, reveals normal epicardial coronaries without significant obstruction due to thrombus or plaque rupture. Left ventriculogram may demonstrate acute ballooning of apical region. LV may assume the shape of Japanese Octopus trap-pot called Takotsubo with narrow apex and round dilated bottom. Takotsubo syndrome thus translates to octopus pot resembling shape of LV during systole on imaging studies. Prognosis is fair in over 90% patients with full recovery of RWMA in 3–6 months. Complications do occur in about 10% cases[2] and in-hospital mortality is estimated as 4.5%.[3] There are no standard guidelines on management of TS.

2. Epidemiology

TS was first described by a Japanese cardiologist in 1990.[4] Many case reports and cases series followed initial description.[5] The disease was initially restricted to Japan but it is now well recognized in Europe, United States, Britain and many other countries. Isolated case reports have been published from France, Belgium, Mexico, Australia, Brazil, Israel, Africa, Turkey and Iceland.[6] Since it is a rare disease, several national and international registries have been established to collect the data on epidemiology, diagnostic criteria and natural course of the disease. A few prominent national registries include Japanese Takotsubo Multicentre Registry from Tokyo CCU Network, German Takotsubo Syndrome Registry, Takotsubo Italian Registry, Nationwide Inpatient Sample (NIS) USA and TS Registry Netherland. The International Takotsubo Registry (Inter TAK Registry) was established at University Hospital, Zurich, Switzerland in 2011 in collaboration of 25 world recognized cardiac centres across seven countries in Europe and US. The incidence of TS remained very low (0.2–0.7%) during the period 2002–2010. With increasing interest on this subject, disease has been recognized more frequently.[7] The incidence is around 1.7–2.2% of all patients initially suspected with ACS and finally diagnosed to have TS. The patients are typically Asian or Caucasian (Asian 57.2%, Caucasian 40% and other races 2.8%). NIS, US recognized 6837 patients of TS in first NIS during 2007–08.[8] The second NIS during 2008–2012 recognized 22005 patients of primary TS and 31942 patients of secondary TS.[9] Inter TAK Registry of Switzerland has indentified 1750 patients of TS during 2012–2014.[10]

3. Aetiology and pathogenesis

The exact aetiology is not known. Normal myocardium utilizes 90% of its energy from fatty acid metabolism and only 10% from glucose metabolism. In TS, there appears to be a shift towards glucose pathway with impaired fatty acid metabolism.

Pathophysiology of TS is complex and involves 'brain heart axis' which is still poorly understood. A significant emotional stress, physical trigger or neurological/psychiatric illness typically precedes the development of TS (Table 1). Over 90% emotional events are negative e.g. death of near relative, motor vehicle accident with psychological trauma, natural disasters, fear, anger on familial conflicts, retirement etc. Such events, leading to TS (labelled as 'broken heart syndrome') are responsible for 90% emotional conflicts.[10] Lesser than 10% of emotional triggers are joyful events like birthday ceremonies, wedding anniversaries, winning a jackpot lottery, unexpected joyful meetings with a friend or relation. The joyful events resulting in TS constitute 'Happy Heart Syndrome'.[11] Many a times the trigger is physical e.g. recent surgery, stay in ICU, stroke, severe psychotic illness, exacerbation of chronic disease like asthma, newly diagnosed serious illness etc. All these emotional and physical events act as triggers which act on heart via brain and stress-induced catecholamine release.

The brain-heart axis involves cortex and subcortical areas including amygdale, hippocampus, basal ganglia and hypothalamus in the initial processing of emotional triggers and results in neuro-hormonal stunning of the myocardium. Intra-cranial pathology, particularly subarachnoid haemorrhage (SAH) may produce clinical picture of TS by neurogenic stunning of myocardium.

Several mechanisms have been proposed to explain the pathogenesis of Takotsubo cardiomyopathy characterized by apical ballooning of left ventricle.

3.1. Catecholamine theory

Due to severe emotional or physical stress, overstimulation of hypothalamus pituitary adrenal axis occurs and results in excessive release of catecholamine. Elevated plasma levels of epinephrine and norepinephrine have been demonstrated during the acute phase.[12] Acute onset of TS and its association with pheochromocytoma or paraganglioma have also suggested that TS may be catecholamine induced myocardial dysfunction.[13] Hypercatecholamines results in myocardial stunning and apical ballooning syndrome (ABS). Histological findings on endomyocardial biopsy of TS show necrosis of contraction bands and infiltration by mononuclear cells. Similar findings are seen in experimental and clinical catecholamine cardiotoxicity.[14,15] Apical portion of LV has the highest concentration of adreno-receptors which explains why catecholamines have maximal effect on the apical portion of the LV resulting in apical akinesia, dilatation and ballooning. Catecholamine excess leads to subtle metabolic changes at cellular level. B2-adrenoreceptor mediated GS proteins signalling (+ve inotropic)

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