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Review

Potential links between neurological disease and Tako-Tsubo cardiomyopathy: A literature review

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ABSTRACT

Tako-Tsubo cardiomyopathy (TTC), is defined as a fully reversible acute deterioration of left-ventricular (LV) function, which is mainly found in women after an episode of emotional or physical stress (e.g. psychosocial stress, sepsis, surgery). The underlying mechanisms remain unclear. There is evidence suggesting a possible link between neurological disease and TTC. The pathophysiology of the several neurologic diseases has been reviewed searching for possible mechanisms that could lead to TTC in these patients.

1. Introduction

Tako-Tsubo cardiomyopathy (TTC), also known as stress induced cardiomyopathy or apical ballooning syndrome (Fig. 1, Video 1), was first described by Dote in 1991 [1]. It is defined as a fully reversible acute deterioration of left-ventricular (LV) function [2], which is mainly found in women after an episode of emotional or physical stress (e.g. psychosocial stress, sepsis, anaphylaxis, surgery) [3–5]. The underlying mechanisms remain unclear, although increased catecholamine levels are considered very important [6–8]. There is evidence suggesting a possible link between neurological disease and TTC. The pathophysiology of the several neurologic diseases has been reviewed searching for possible mechanisms that could lead to TTC in these patients.

2. Methods

We identified relevant English-language publications through a PubMed search using the keywords 'Tako-Tsubo cardiomyopathy', 'stress induced cardiomyopathy', and 'apical ballooning syndrome' in November 2012 in different combinations with: stroke, intracranial hemorrhage, subarachnoid hemorrhage, epilepsy, seizure, amyotrophic lateral sclerosis, Parkinson and Alzheimer diseases. We completed this search by cross-referencing published articles and also performed a hand search of major journals. We have restricted the citations to the most relevant and informative publications.

3. Stroke

Stroke is classified in two three main typologies: ischemic stroke (the most common 80%), intraparenchymal hemorrhage (17%) and sub-arachnoid hemorrhage (SAH) (3%) [9].

3.1. Ischemic stroke

There are several possible links with TTC that could be cause and effect of ischemic stroke. The dysfunction of central autonomic network associated with cerebral infarction, especially involving the territory of middle cerebral artery or basilar artery could cause TTC [10], linked to catecholamine excess [11]. In case series among patients who presented with acute ischemic stroke, 1.2% developed TTC, with stroke acting as the culprit "stressor" [12]. It most often occurred soon after stroke onset and was commonly asymptomatic. Female sex and insular damage were predominant features of the stroke patients who experienced TTC. Extensive brainstem ischemia with autonomic disturbances was considered as leading to TTC.

By contrast, LV dysfunction in TTC, as in myocardial infarction, can lead LV thrombi formation with consequent cerebral embolism, responsible of cardio-embolic stroke [13]. LV thrombosis is a relatively frequent complication in patients with severe ischemic heart disease affecting 13 to 20% of these patients [14,15]. In TTC the main cause responsible for LV thrombosis is the reduced blood flow in LV apex during apical ballooning; other (co)factors, however (S- or C-protein deficiency, C-reactive protein, platelet aggregation, hormone levels, genetic factors) were suggested. A recent review estimates the incidence

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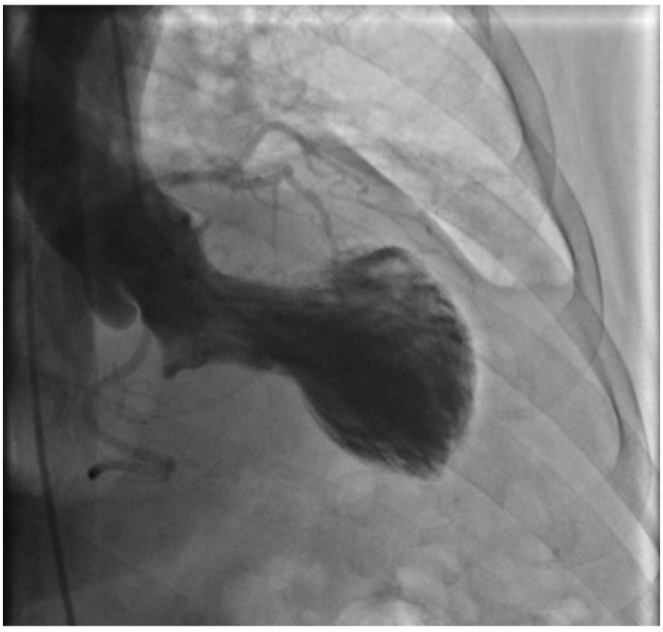

Fig. 1. Typical aspect of left ventricular apical ballooning in a patient with amyotrophic lateral sclerosis (systole) and Tako-Tsubo cardiomyopathy.

of LV thrombo-embolism in TTC of about 2.5% [16]. The LV thrombo-embolism in TTC seems to have a favorable prognosis, although an appropriate treatment with anticoagulants should be adopted after a prompt diagnosis.

3.2. Hemorrhagic stroke

Intracranial hemorrhage is commonly related to higher levels of catecholamines for an upregulation of the sympathetic system to assure brain perfusion [17] during intracerebral hypertension. In normal untreated mice, experimental intracranial hemorrhage produced myocardial damage. However, adrenalectomy reduced the incidence of myocardial damage after intracranial hemorrhage [18]. This postulated mechanism is supported by the fact that a genetic tendency to increased catecholamine sensitivity is associated with an increased risk of cardiac abnormalities following SAH [19].

SAH commonly produces ECG abnormalities which are attributed to effects of catecholamines on the myocardium as presence of U waves, T wave abnormalities and prolongation of QT interval, as well as atrial and ventricular arrhythmias [20]. Recent studies linked apico-basal gradient of LV myocardial edema to transient T-wave inversion and QT-interval prolongation in TTC [21]. Moreover LV wall motion abnormalities were detected in 18% of patients with SAH and higher incidence 35% in those with Hunt & Hess grades 3–5 [22].

Twenty-one cases of SAH associated to TTC were reported [23–26], one with occurrence of cardiogenic shock requiring intra aortic pumping [27] and two cases of inverted TTC [28,29]. The incidence of TTC in SAH patients amounts to 1.2% [30].

4. Epilepsy

Convulsive status epilepticus is typically associated with marked increases in plasma catecholamines (particularly during the phase of generalized seizures and even after several hours) [31]. The increased plasma norepinephrine concentrations are presumably due to activation of peripheral adrenergic neurons. This seems to be mediated primarily by electrical excitation of the brain. However, muscular hyperactivity may also contribute; the increment in plasma norepinephrine is greater in the absence of paralysis and its rise in circulating indicates adrenergic activation. The levels of norepinephrine reached in the first 10 min are sufficient to exert a direct vasoconstrictor effect [32]. It means that even a simple tonic clonic seizure could be responsible of elevated circulating levels of catecholamines, although their concentrations declined within 30 min [32]. This condition is accompanied by changes in cardiovascular function that could account for many of the sudden, unexpected, and unexplained death that occurs in epileptic people [33]; the increases in plasma epinephrine concentration during a generalized seizure may, in some patients, be large enough to cause cardiac arrhythmias [34].

An excessive release of catecholamines seems to have a pivotal role in the development of TTC during epileptic seizures and could explain the severe clinical course of seizure-associated TTC [35]. As reported by Stöllberger [36] TTC is linked to different kinds of seizures: tonic–clonic, generalized and status epilepticus. Compared with a group control of TTC patient without seizures, patients with seizure-associated TTC were younger, more frequently male, had less frequent chest-pain, a higher rate of recurrence and a higher rate of cardiogenic shock. Chest pain, a common clinical sign of TTC, is rarely reported in seizure-associated TTC, and could be due to postictally impaired consciousness or due to sedation from emergency antiepileptic treatment. The clinical manifestation of TTC in these patients is a sudden hemodynamic deterioration either due to pump failure or due to arrhythmia. TTC after epilepsy may be relatively common; its estimated incidence is about 1% [37].

5. Neurodegenerative diseases

Neurodegenerative diseases represent a heterogeneous group of distinct nosographic entities, linked by similar pathogenic and clinical features: Alzheimer, Parkinson, Parkinson-plus, amyotrophic lateral sclerosis, Huntington's disease, and fronto-temporal dementia. The exact etiology is not yet defined, even if in a few cases genetic mutations have been identified. These conditions are characterized by a chronic and selective process of neuronal death [38] and by a deposition of misfolded proteins (alpha beta-peptide, alpha-synuclein and Cu, Zn superoxide dismutase) with following oxidative stress [39]. That is accompanied by diminished levels of catecholamines in neuronal tissue and increased in systemic flow. Some studies hypothesized that catecholamines might act as scavengers of free radicals in neuronal tissue, and that could stimulate an increased systemic production [40] (Table 1).

5.1. Alzheimer disease

Alzheimer disease is the most common neurodegenerative disease (50–55% of people with dementia are affected by Alzheimer disease). Increasing evidence suggests a role, in its pathogenesis, of mitochondrial dysfunction, microglial activation and insulin resistance. Oxidative stress is present early in pathogenesis and contributes to disease progression. It occurs when the generation of reactive oxygen species (ROS) in a system exceeds the system's ability to neutralize and eliminate them. Also inflammation can induce oxidative damage, especially via microglia, leading to increased ROS formation and the resulting damage to lipid, proteins, and nucleic acids [41]. In this context several strategies could be adopted in order to reduce oxidative stress; a larger catecholamine consumption in neuronal tissue might act as an antioxidant; conversely, lower levels of catecholamines were found in urine of Alzheimer disease patients when compared with healthy volunteers [42].

Just one case is reported in literature of TTC in a patient with Alzheimer disease [43]. An 80-year-old woman showed clinical symptoms of chest pain, electrocardiographic changes, elevated myocardial markers, and transient LV apical ballooning in the absence of significant coronary artery disease.