International Journal of Cardiology 177 (2014) 322–329

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

CNS disease triggering Takotsubo stress cardiomyopathy ☆

Josef Finsterer [a,*], Karim Wahbi [b,c,d]

[a] Krankenanstalt Rudolfstiftung, Vienna, Austria
[b] Paris-Descartes, Sorbonne Paris Cite University, 75006 Paris, France
[c] AP-HP, Cardiology Department, Cochin Hospital, Paris, France
[d] AP-HP, Neurology Department, Pitié-Salpêtrière Hospital, Paris, France

ARTICLE INFO

Article history:
Received 24 June 2014
Accepted 17 August 2014
Available online 26 August 2014

Keywords:
Genetics
Hereditary disease
Cardiac involvement
Brain heart disorder
Broken heart syndrome
Stress cardiomyopathy

ABSTRACT

There are a number of hereditary and non-hereditary central nervous system (CNS) disorders, which directly or indirectly affect the heart (brain–heart disorders). The most well-known of these CNS disorders are epilepsy, stroke, infectious or immunological encephalitis/meningitis, migraine, and traumatic brain injury. In addition, a number of hereditary and non-hereditary neurodegenerative disorders may impair cardiac functions. Affection of the heart may manifest not only as arrhythmias, myocardial infarction, autonomic impairment, systolic dysfunction/heart failure, arterial hypertension, or pulmonary hypertension, but also as stress cardiomyopathy (Takotsubo syndrome, TTS). CNS disease triggering TTS includes subarachnoid bleeding, epilepsy, ischemic stroke, intracerebral bleeding, migraine, encephalitis, traumatic brain injury, PRES syndrome, or ALS. Usually, TTS is acutely precipitated by stress triggered by various different events. TTS is one of the cardiac abnormalities most frequently induced by CNS disorders. Appropriate management of TTS from CNS disorders is essential to improve the outcome of affected patients.

1. Introduction

Central nervous system (CNS) disease may cause a number of cardiac abnormalities (brain–heart disorders (BHDs)) which may include stress cardiomyopathy, also known as Takotsubo syndrome (TTS), apical ballooning, Takotsubo cardiomyopathy, broken–heart syndrome, transient regional left ventricular dysfunction, transient myocardial dysfunction (MI), transient systolic dysfunction, neurogenic stunned myocardium, neurogenic stressed myocardium, catecholamine cardiomyopathy, neurogenic stress cardiomyopathy, or reversible acute heart failure [1]. The mechanism by which CNS disease induces TTS is most likely catecholamine stress induced by fear, pain, or anxiety [2]. This mini-review aims at providing an overview about the current knowledge concerning CNS disorders triggering TTS.

2. Method

Data for this review were identified by searches in MEDLINE, Current Contents, and references from relevant articles using the search terms "central nervous system", "cerebral", "brain", "autonomous nervous system", "sympathetic", "parasympathetic", "stroke", "intracerebral bleeding", "subarachnoid bleeding", "seizure", "epilepsy", "traumatic brain injury", "migraine", "central sleep apnea syndrome", "restless leg syndrome", "Parkinson syndrome", and "amyotrophic lateral sclerosis" in combination with "stress cardiomyopathy", "transient systolic dysfunction", "reversible acute heart failure", "broken heart syndrome", "Takotsubo syndrome", "neurogenic stunned myocardium", "neurogenic stressed myocardium", and "apical ballooning". Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles published in English between 1966 and 2014 were considered. Appropriate papers were studied and discussed for their suitability to be incorporated in this review. Transient regional left ventricular dysfunction, neurogenic stunned myocardium, and neurogenic stressed myocardium were not differentiated from classical TTS as they can be regarded as the same entity [3].

3. Results

3.1. Definition

Various attempts have been undertaken to unambiguously describe and define TTS. These efforts resulted in the creation of the Mayo Clinic Criteria, the revised Mayo Clinic Criteria, the criteria of the Japanese Circulation Society, the John Hopkins criteria, and the Madias criteria [4]. The American Heart Association (AHA) and the European Heart Association (EHA) follow in their cardiomyopathy guidelines these criteria and classify TTS as an unclassified cardiomyopathy characterized by transient akinesia/hypokinesia of the apex (classical TTS), the midventricular segments, or the basal segments (inverted TTS) with systolic dysfunction in the acute phase and typical imaging features of apical ballooning (in case of the apical form), typical ECG abnormalities (ST-elevation, negative T-waves), CK and troponin T elevation, with or without anginal chest pain [5]. Inverted TTS is characterized by basal and

☆ Contribution of authors: JF designed the review, organized the literature, and wrote the first draft of the manuscript. KW completed the literature search, supported in the writing, and provided critical comments.

* Corresponding author at: Schindlergasse 9/10, 1180 Vienna, Austria. Tel.: +43 1 71165 92085; fax: +43 1 4781711.
E-mail address: fifigs1@yahoo.de (J. Finsterer).

http://dx.doi.org/10.1016/j.ijcard.2014.08.101
0167-5273/

mid-ventricular segmental hypokinesia/akinesia but hyperdynamic apical segments, a pattern not associated with a coronary artery distribution. The most frequent of the three morphological TTS types is the apical form. TTS mimics myocardial infarction (MI) clinically and electrocardiographically with the difference that all cardiac abnormalities in TTS are transient and disappear within a few weeks (echocardiography after approximately 6 weeks, ECG approximately after 10 weeks) after onset and that the coronary arteries are usually normal on coronary angiography.

3.2. Causes

Though the pathophysiology of TTS is not fully clarified, there is evidence that TTS is a phenomenon typically induced by stress triggered by various different conditions, which is reflected by the many different terms, used to describe TTS. TTS has been also discussed as a cause of SUDEP syndrome [6]. Pathogenetic mechanisms discussed to explain TTS include multi-vessel coronary spasm, myocardial microvascular dysfunction, aborted MI caused by transient thrombotic occlusion of a wrapped-around left anterior descending artery, left ventricular outflow tract obstruction, blood-borne catecholamine cardiac toxicity, or cardiac sympathetic disruption with nor-epinephrine seethe and spillover [7]. Arguments for catecholamine toxicity are that serum nor-epinephrine and epinephrine are increased during the first week after SAB to normalize by 6 months after the event [8] and that patients with prolonged seizures or epileptic state have elevated nor-adrenaline serum levels, which remain elevated during several hours after the event [9]. The role of increased catecholamines is substantiated by TTS models showing the prevention of contraction band necrosis by cardiac sympathectomy or cardiac denervation but not by vagotomy or bilateral adrenalectomy [10].

3.3. Clinical manifestations and pathological changes

TTS may be asymptomatic or symptomatic. The most frequent symptoms of TTS include chest pain or dyspnea. About two thirds of the patients complain about chest pain on admission. Depending on the severity and number of complications, additional symptoms include palpitations, syncope, weakness, cough, fever, nausea, vomiting, fear, tiredness, or edema [11]. Complete recovery is on the average achieved within 12 ± 3 days after onset [12]. A strong preference for postmenopausal females is well established [13]. In a retrospective survey of 24,701 patients with TTS almost 90% were female [13]. Serial myocardial biopsies in the acute phase show hypertrophy of cardiomyocytes due to an abnormally increased number of vacuoles, intracellular accumulation of glycogen, and disorganization of contractile and cytoskeletal proteins. Extracellular matrix proteins are increased [12].

3.4. Diagnosis

TTS is diagnosed by taking the individual and family history, by clinical cardiologic exam, ECG, echocardiography, coronary angiography, and by regular follow-up investigations until complete recovery of the cardiac abnormalities. Usually, TTS is diagnosed according to the revised Mayo Clinic Criteria, which include 1) chest pain with transient left ventricular wall motion abnormalities involving the apical, mid-ventricular, or basal myocardial segments extending beyond a single epicardial coronary artery distribution (regional wall motion abnormality in a non-vascular pattern) on echocardiography or cardiac MRI; 2) absence of obstructive epicardial coronary artery disease that could be responsible for the observed wall motion abnormality; 3) ECG abnormalities mimicking MI, such as transient ST-segment elevation or diffuse T-wave inversion associated with mild creatine-kinase or troponin elevation; 4) the lack of proven pheochromocytoma or myocarditis [14], and 5) ECG dynamics with the development of negative T-waves, and normalization of the echocardiographic findings by 6 weeks and of the ECG abnormalities by 10 weeks. Often it is impossible to decide if the CNS disorder was truly present before the TTS or vice versa, since CNS disease may be also a complication of TTS [15,16].

3.5. Treatment

Treatment of TTS is generally supportive and includes avoiding or minimizing the exposure of the patient towards further stress and the prescription of drugs. Drugs used for TTS include β-blockers or calcium antagonists, diuretics, and in case of severe hypokinesia/akinesia, oral anticoagulation with vitamin-K antagonists to prevent intra-cardiac thrombus formation. Acetyl-salicylic acid may be helpful if there is concomitant coronary atherosclerosis [11]. Although TTS patients are usually hypotone, inotropes should be avoided since they may fuel TTS due to the already high serum catecholamine concentrations. In 1% of the cases an intra-aortic balloon pump may be indicated [17,18]. Ventricular assist devices may be another option.

3.6. Outcome

TTS is, in the majority of the cases, a transient abnormality with complete recovery within a few days or maximally 3 months. In some of the cases, however, TTS may not resolve and may be associated with complications or may take a fatal course (Table 1) [19]. Serious complications of TTS may occur in single cases and include severe rhythm abnormalities (QT-prolongation, ventricular tachycardias (VTs), sudden cardiac death (SCD)) [20], non-reversible acute heart failure [21], intraventricular thrombus formation [22], MI [23], ventricular rupture [24], or cardiogenic shock. Non-cardiac complications of TTS include sepsis, pulmonary edema, anemia, stroke or peripheral embolism, or rhabdomyolysis [5]. Occurrence of any of these complications may worsen the outcome of TTS [20]. Generally, the outcome is favorable with the classical form while being poor with the inverted type [25].

3.7. CNS disorders inducing TTS

CNS disease triggering TTS are numerous and include subarachnoid bleeding (SAB) [14], epilepsy [26], ischemic stroke [27,28], intra-

Table 1
Subarachnoid bleeding triggering TTS.

CNS disease	NOP	FMR	AR	TTST	OC	Reference
Subarachnoid bleeding	49	80% f	∅55	nm	nm	[14]
Subarachnoid bleeding	18	15 f. 3 m	nm	nm	FR	[35]
Subarachnoid bleeding	8	7 f. 1 m	∅47	nm	FR	[18]
Subarachnoid bleeding	8	f	∅55.5	Classic	nm	[37]
Subarachnoid bleeding	4	f	43–67	Inverted	nm	[25]
Subarachnoid bleeding	2	nm	nm	Mid, basal	nm	[48]
Subarachnoid bleeding	1	f	48	Classic	FR	[38]
Subarachnoid bleeding	1	f	46	Inverted	FR	[39]
Subarachnoid bleeding	1	nm	nm	Classic	FR	[36]
Subarachnoid bleeding	1	f	65	Classic	FR	[40]
Subarachnoid bleeding	1	f	40	Inverted	Death	[41]
Subarachnoid bleeding	1	f	64	Mid	Death	[42]
Subarachnoid bleeding	1	f	nm	Classic	nm	[43]
Subarachnoid bleeding	1	f	77	Classic	FR	[44]
Subarachnoid bleeding	1	m	57	Classic	Death	[45]
Subarachnoid bleeding	1	f	67	Classic	FR	[46]
Subarachnoid bleeding	1	f	48	Inverted	Death	[49]
Subarachnoid bleeding	1	f	90	Classic	FR	[47]
Subarachnoid bleeding	1	f	64	Classic	nm	[50]
Subarachnoid bleeding	1	f	69	Classic	nm	[51]
Subarachnoid bleeding	1	m	29	Inverted	Death	[97]
Subarachnoid bleeding	1	m	63	Classic	Death	[154]
Subarachnoid bleeding	1	f	57	nm	FR	[155]
Subarachnoid bleeding	1	nm	57	Classic	FR	[156]
Subarachnoid bleeding	1	f	40	Classic	FR	[157]

NOP: number of patients, FMR: female to male ratio, AR: age range, TTST: TTS-type, OC: outcome, f: female, m: male, FR: full recovery, nm: not mentioned.