Review

The relationship between takotsubo syndrome, left ventricular hypertrabeculation/noncompaction, neurologic and neuromuscular disorders

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Takotsubo syndrome (TTS) and left ventricular hypertrabeculation/noncompaction (LVHT) have in common that they are only diagnosed since 1990. Diagnostic criteria and prognosis of affected patients are still debated and the knowledge about etiology and pathogenesis of both disorders is limited. Both abnormalities are associated with neurologic and neuromuscular disorders (NMD). We summarize the data about the relationship between TTS, LVHT and NMD. We identified 8 case reports about the co-incidence of TTS and LVHT (6 females, 2 males, age 0–76 years). In 2/8 cases recurrent TTS occurred after 8 and 10 months. In most of the patients, LVHT was diagnosed together with TTS, thus, it cannot be assessed if LVHT was present since birth or developed during life-time. In one case, LVHT was absent in a previous echocardiogram, developed *de novo* during TTS, and disappeared after 3 months. In 4/8 patients follow-up were reported, and in all of them, regression or disappearance of LVHT was observed. NMD or psychiatric disorders were reported in 7/8 patients. We conclude —limited by the small number of cases—that patients with LVHT and TTS seem to be frequently associated with NMD and have a high risk of recurrence. LVHT seems to disappear after TTS, but it remains unclear whether trabeculations in fact regress or are still present, but not more visible because of a decrease in left ventricular size resulting in smaller spaces between the trabeculations. Patients with LVHT and TTS require long-term follow-up to assess any changes of these abnormalities over time.

Keywords

Transient left ventricular dysfunction; Stress cardiomyopathy; Noncompaction; Neurology; Neuromuscular disorders

1. Introduction

1.1 Aim of the review

Takotsubo syndrome (TTS) and left ventricular hypertrabeculation/noncompaction (LVHT) have in common that they are relatively rare cardiac abnormalities and that they are only diagnosed since 1990 [1, 2]. Because of the relative newness, diagnostic criteria and prognosis of affected patients are still debated and the knowledge about etiology and pathogenesis of both disorders is limited [3, 4]. The left ventricular apex is frequently involved in LVHT as well as in TTS, and both abnormalities are associated with neurologic and neuromuscular disorders (NMD) [5–8]. It is unknown if LVHT and TTS have a causal relationship. We summarize the data about the relationship between TTS, LVHT and NMD.

1.2 Methods

We screened the literature using PubMed from January 2000 to September 2021 by using the terms "takotsubo" "tako tsubo", tako-tsubo", "apical ballooning", "transient left ventricular dysfunction", "stress cardiomyopathy", "stunned myocardium", "ventricular ballooning", "broken heart" or "broken-heart", and "noncompaction", "non-compaction" or "hypertrabeculation". We combined all search terms for TTS and LVHT. Both authors screened the titles and abstracts independent from each other, identified and read articles of interest in full text. We considered articles in English and German language. The references of the articles of interest were checked for further potential relevant articles. We planned to include cohort studies, case series and case reports.

The following characteristics were collected from the included articles: Age and gender of the reported patients, diagnostic criteria for TTS, pharmacotherapy on admission, TTS trigger, NMD or psychiatric disease, time of diagnosis of LVHT, in-hospital outcome, long-term outcome and change of LVHT at follow-up.

2. Left ventricular hypertrabeculation/noncompaction

2.1 Anatomic definition

The human left ventricle has a smooth endocardial surface. Anatomic inspection of the inside of the left normal ventricle discloses papillary muscles and — occasionally — false tendons and aberrant bands — and up to three prominent left ventricular trabeculations are found [9]. In rare cases, more than three trabeculations with intertrabecular recesses are found in the left ventricle (Fig. 1A) [10]. Different names, such as "left ventricular hypertrabeculation", "noncompaction" or "persisting sinusoids" are used for this abnormality. We prefer the purely descriptive term LVHT.

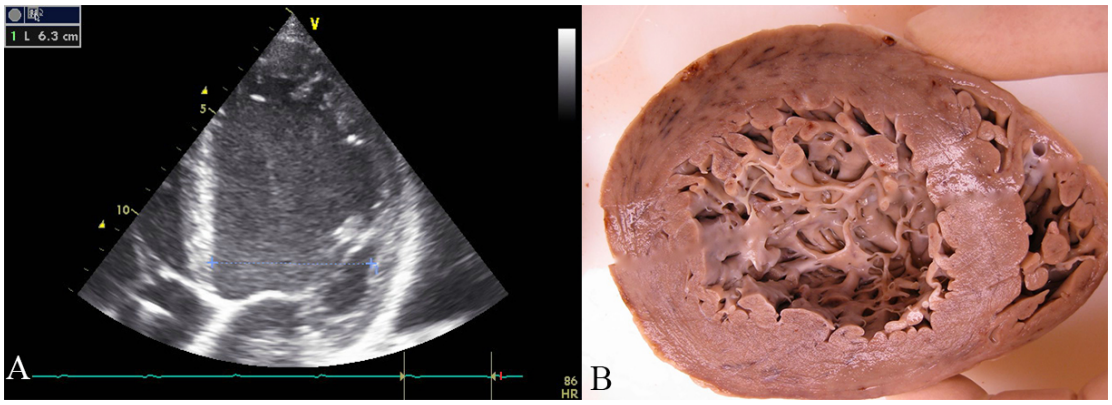

Fig. 1. Echocardiographic and pathoanatomic picture of left ventricular hypertrabeculation/noncompaction. (A) Echocardiographic apical four-chamber-view of a patient with dilated cardiomyopathy. Four trabeculations are visible in the apex of the left ventricle, thus fulfilling the criteria of Stöllberger *et al.* [10] for left ventricular hypertrabeculation/noncompaction. (B) One week after echocardiography, the patient died due to heart failure. The formaldehyde-fixed heart is opened along the short axis. A heavily trabeculated apical portion of the left ventricle is visible.

2.2 Diagnosis by imaging methods

Transthoracic echocardiography is the most frequently applied method for diagnosing LVHT because it is non-invasive, without radiation, needs usually no contrast medium, widely available and unexpensive. Echocardiography, on the other side, has disadvantages because it is highly dependent on the experience of the investigator. The image quality may be impeded, especially in the apical region, where LVHT is frequently located (Fig. 1B). Thus, by echocardiography, LVHT may be over- as well as under-diagnosed [4]. Currently, different echocardiographic criteria are used and their application may influence the prevalence of LVHT (Table 1, Ref. [2, 11, 12]). A further problem in diagnosing LVHT by echocardiography is the poor inter- and intra-observer agreement, especially when investigators from different laboratories are compared [13].

Due to the high image resolution, cardiac magnetic resonance imaging (cMRI) visualizes the apical regions more accurately than echocardiography. Also for cMRI, different diagnostic criteria for LVHT co-exist (Table 1, Ref. [14–19]). Whereas the diagnosis of LVHT by cMRI seems to have a higher inter- and intra-observer agreement than echocardiography, the currently used criteria are challenged because of over-diagnosing which results in a high prevalence of LVHT among asymptomatic individuals [20].

2.3 Clinical manifestations, therapy and prognosis

LVHT has been described as an isolated abnormality or associated with congenital cardiac disorders, in normally sized ventricles with good systolic function, in dilated ventricles with systolic dysfunction or in ventricles with left ventricular wall thickening. LVHT may be clinically silent, but also manifest with congestive heart failure, arrhythmias, arterial embolism and sudden cardiac death. Initially, based on the publication of the first few cases, it was assumed that LVHT is a cardiac disease with a dismal prognosis [2]. Observation of larger cohorts with a longer follow-up period, allowed to find risk factors for adverse outcomes like increased age, NMD, congestive heart failure, systolic dysfunction and atrial fibrillation [8, 21]. Initially, LVHT was assumed to be a congenital abnormality, however, in the meantime also patients with acquired LVHT have been reported, and development of LVHT has been described in healthy females during pregnancy [7, 22].

No specific therapy-recommendations exist for patients with LVHT. Clinical manifestations like systolic dysfunction or arrhythmias should be treated according to appropriate guidelines [23, 24].

3. Neurologic and neuromuscular disorders

NMD can be detected in up to 80% of LVHT-patients, when they are systematically referred to a neurologist, irrespective of clinical signs for NMD, visible for a cardiologist [12]. Most frequently associated with LVHT are mitochondrial disorders, Barth syndrome, zaspopathy, myotonic dystrophy type 1, dystrobrevinopathy and Emery-Dreifuss muscular dystrophy owing to LMNA mutations [7].

The association between LVHT and NMD are, so far, unclear. Arguments against a causal relationship include the observation that LVHT can be found in only a small number of patients with a particular NMD, even if patients with NMD are systematically screened for LVHT, and that the variety of different NMD associated with LVHT is large, suggesting that LVHT results from a compensatory rather than a genetic mechanism [7].

More than 100 gene variants have been identified in LVHT and seem to play a role in the pathogenesis of LVHT [21, 25]. A considerable overlap in the pathogenesis of LVHT with other cardiomyopathies seems to exist since mutations in genes, found in LVHT-patients, are also identified in patients with hypertrophic or dilated cardiomyopathies, arrhythmias, myopathies, developmental defects or mitochondrial disorders [25].

Table 1. Definitions of left ventricular hypertrabeculation/noncompaction by echocardiography and magnetic resonance imaging.

Author	Chin *et al.* [2]	Jenni *et al.* [11]	Stöllberger *et al.* [12]	Petersen *et al.* [14]	Stacey *et al.* [15]	Jacquier *et al.* [16]	Captur *et al.* [17]	Choi *et al.* [18]	Grothoff *et al.* [19]
Technique	Echo	Echo	Echo	cMRI	cMRI	cMRI	cMRI	cMRI	cMRI
Number of trabeculations	NM	NM	>3	NM	NM	NM	NM	NM	NM
X/Y ratio	<0.5	NM	NM	NM	NM	NM	NM	NM	NM
NC/C ratio in end-diastole	NM	NM	NM	>2.3	>3	NM	>2.3	>2.3	>2.3
NC/C ratio in end-systole	NM	>2.0	NM	NM	>2	NM	NM	NM	NM
Trabeculated/LV mass	NM	NM	NM	NM	NM	>20%	>20%	>35%	>25%
NC layer >50% of LV thickness	NM	NM	NM	NM	NM	NM	NM	NM	NM
Apical FD	NM	NM	NM	NM	NM	NM	>1.3	NM	NM
Two-layered myocardium	yes	yes	yes	yes	yes	yes	yes	yes	yes
ITRPFV	NM	yes	yes	NM	NM	NM	NM	NM	NM
No other cardiac abnormality	NM	yes	NM	NM	NM	NM	NM	NM	NM
Poorly developed PM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Anatomically controlled	3/8	8/17	12/12	no	no	no	no	no	no
IOV agreement studies	a	a	a, s	a	s	a, s	s, a	s	no

a, IOV agreement studies assessed by the authors of the definition; C, compacted myocardial layer thickness; cMRI, cardiac magnetic resonance imaging; Echo, echocardiography; FD, fractal dimension; IOV, inter/intra-observer; ITRPFV, intertrabecular perfusion from the ventricular side; LV, left ventricle; NC, noncompacted myocardial layer thickness; NM, not mentioned; PM, papillary muscles; s, IOV agreement studies assessed by the authors of the definition; X/Y ratio, ratio of the distance between epicardial surface and trough of the intertrabecular recesses (X) and the distance between epicardial surface and peak of the trabeculations (Y).

Since the prognosis of patients with LVHT seems to be dependent on presence or absence of NMD, we strongly recommend a neurologic investigation to search for NMD after the diagnosis of LVHT is established [8]. Only in cases with an obvious genetic background, molecular studies should be considered.

4. Takotsubo syndrome

4.1 Definition

TTS is a transient left ventricular dysfunction leading to acute heart failure which mimics an acute coronary syndrome, and has a similar outcome [6, 26, 27]. The pathophysiology of TTS is incompletely clarified and not fully understood. In TTS patients, specific alterations in neurological response and sympathetic activation after emotional stimuli have been demonstrated [28].

Different definitions for TTS are used in the literature (Table 2, Ref. [26, 29–31]). Based on the location of the LV movement pattern, observed by echocardiography or ventriculography, TTS is classified into four different types: apical, midventricular, basal ballooning and focal wall motion patterns. Apical ballooning is the most frequent type occurring in 80% of TTS patients [26].

4.2 Pathophysiology

In the pathophysiology of TTS, catecholamines appear to play an important role. The trigger of TTS is often a sudden emotional stress. Physical triggers can also lead to extreme sympathetic activation. Brain areas associated with sympathetic autonomic tone seem to be involved in the pathogenesis of TTS [28]. Three pathophysiological aspects are to consider: (1) The stress answer of the cognitive centres of the brain and hypothalamic–pituitary-adrenal axis, and how much epinephrine and norepinephrine are released, (2) the response of the myocardium, coronary arteries, and peripheral arterial and venous system to the sudden sympathetic activation and surge in circulating catecholamines, and (3) the response of the sympathetic nervous system [26].

4.3 Clinical manifestations, therapy and prognosis

Symptoms, acute complications and in-hospital mortality of TTS are not different from acute myocardial infarction [6, 27, 32]. Initially believed to have a good prognosis, evidence has accumulated that TTS is not a benign condition because of long-term mortality, recurrent TTS, associated comorbidities and sudden cardiac death [32].

There are no randomized clinical trials about treatment of TTS-patients. Retrospective registries suggest that therapy with angiotensin converting enzyme inhibitors and angiotensin-receptor blockers might by associated with improved survival at one-year follow-up in TTS-patients with or without heart failure [6]. Whether beta-blockers protect against recurrent TTS, is controversially discussed [6, 33, 34]. Probably, there is a role for beta-blockers in TTS-patients with persistently elevated sympathetic tone, increased anxiety and recurrent TTS [26, 33]. Pharmacotherapy should be prescribed and adapted considering the hemodynamic situation and cardiovascular comorbidities.

Table 2. Diagnostic criteria for takotsubo syndrome.

Characteristic	Mayo Clinic, 2008 [29]	Italian Network, 2014 [30]	ESC Heart failure Association Taskforce, 2016 [26]	InterTak Registry, 2018 [31]
Transient wall motion abnormality	+	+	+	+
Stress as trigger	+	Optional	+	+
Neurological trigger	NM	NM	NM	+
Coronary arteries	No obstruction	No obstruction	No obstruction	Atherosclerosis can coexist
New ECG abnormalities	+	+	+	+
Cardiac biomarkers	Troponin	Creatinekinase	Troponin, BNP	Troponin, creatinekinase, BNP
No evidence of myocarditis	+	+	NM	+
No evidence of phaeochromocytoma	+	NM	NM	NM
Postmenopausal women	NM	Optional	NM	+

NM, not mentioned; ECG, electrocardiogram; BNP, Brain natriuretic peptide.

Table 3. Neurological and neuromuscular comorbidities in patients with Takotsubo syndrome, according to the literature [5, 35–37].

Trigger	Incidence	Level of evidence
Disorder (in alphabetical order)		
Acute myelitis	Rare	Case reports
Amyotrophic lateral sclerosis	Rare	Case reports
Autonomic neuropathy	Rare	Case reports
Beals syndrome	Rare	Case reports
Brain tumor	Rare	Case reports
Cerebral arterio-venous fistula	Rare	Case reports
Cerebral hypoxia	Rare	Case reports
Chiari-I-malformation	Rare	Case reports
Cyclic vomiting syndrome	Rare	Case reports
Dementia	Rare	Case reports
Guillain-Barre syndrome	Rare	Case reports
Hereditary motor and sensory neuropathy	Rare	Case reports
Hydrocephalus	Rare	Case reports
Hypokalemia-related myopathy	Rare	Case reports
Intracerebral hemorrhage	Frequent	Cohort studies
Ischemic stroke	Frequent	Cohort studies
Meningitis/encephalitis	Rare	Cohort studies
Metabolic myopathy	Rare	Case reports
Migraine	Rare	Cohort studies
Mitochondrial disorder	Rare	Case reports
Multiple sclerosis	Rare	Case reports
Myasthenia gravis	Rare	Case reports
Parkinsonism	Rare	Case reports
Polymyalgia rheumatica	Rare	Case reports
Posterior reversible encephalopathy syndrome	Rare	Case reports
Rhabdomyolysis	Rare	Case reports
Seizures	Frequent	Cohort studies
Serotonin syndrome	Rare	Case reports
Subarachnoid hemorrhage	Frequent	Cohort studies
Neuroleptic malignant syndrome	Rare	Case reports
Transient global amnesia	Rare	Cohort studies
Traumatic brain injury	Rare	Case reports
Botulism	Rare	Case report

Table 4. Cases with Takotsubo syndrome and left ventricular hypertrabeculation/noncompaction.

Author	Age/Sex	TTS confirmed	Pharmacotherapy on admission	TTS trigger	NMD or psychiatric disease	LVHT known before TTS	In-hospital outcome	Long-term outcome	Change of LVHT
Matsumoto *et al.* [38]	Newborn/m	In part*	None	Unknown	Beals syndrome	No	No event	No event after 1 month	Regression after 1 month
Karamitsos *et al.* [39]	76/f	Yes	NR	Playing croquet	NI	No	No event	No event after 2 months	Disappeared after 2 months
De Rosa *et al.* [40]	12/f	In part*	None	Hydrocephalus	Intracranial astrocytoma	No	No event	No event after 12 months	Disappeared after 15 days
Güvenç *et al.* [41]	20/m	Yes	None	Unknown	NI	No	No event	NR	NR
Finsterer *et al.* [42]	47/f	Yes, recurrent, 10 months before	NR	Surgery, respiratory infection	Myotonic dystrophy 1	No	Died due to septic shock one day after the second TTS	NA	NA
Del Buono *et al.* [44]	61/f	Yes, recurrent, 8 months before	None	Emotional stress	Anxiety	No	No event	NR	NR
Finsterer *et al.* [43]	68/f	Yes	NR	Offended of being unable to sing	Unspecified NMD, Panic attack	Yes, since 7 years	No event	No event after 2 years	NR
Kato *et al.* [45]	9/f	In part*	None	Ventriculo-peritoneal shunt dysfunction	Neonatal posthaemorrhagic hydrocephalus	No	No event	No event	Disappeared after 3 months

f, Female; LVHT, left ventricular hypertrabeculation/noncompaction; m, Male; NA, not applicable; NI, not investigated; NMD, neurological or neuromuscular disorder; NR, not reported; *, No coronary angiography was carried out; TTS, Takotsubo syndrome.

5. Neurologic and neuromuscular disorders

Many NMD are reported in association with TTS (Table 3, Ref. [5, 35–37]). Presence or absence of a NMD or psychiatric disorder is one of several components of the InterTak diagnostic score for TTS [31]. Nevertheless, it is largely unknown whether a NMD renders a patient more prone to TTS than a patient without a NMD. Several NMD can be triggers of TTS, such as subarachnoid bleeding, seizures, myasthenia, or migraine. Stroke can be a trigger as well as a consequence of TTS due to thrombus formation and subsequent embolization from the hypokinetic left ventricle. There are also patients, however, with NMD and TTS in whom no explanation for the coincidence of both disorders can be detected.

6. Co-incidence of TTS and LVHT

6.1 Results of literature research

We did neither find cohort studies about the incidence of TTS in LVHT nor about the incidence of LVHT in TTS. We identified 8 case reports about the co-incidence of TTS and LVHT, as listed in Table 4 (Ref. [38–45]). The reported cases comprise 6 female and 2 male patients with an age range from zero to 76 years. Five of the 8 cases fulfilled diagnostic criteria for TTS, as listed in Table 2, in the remaining 3 children, no coronary angiography was carried out. In 2 of the 8 cases, recurrent TTS was described, occurring after 8 and 10 months [42, 44]. Whether TTS occurred under pharmacotherapy remains unclear in 3 patients, in the remaining 5, it occurred without pharmacotherapy (Table 4). In most of the patients, LVHT was diagnosed together with the TTS, thus, it cannot be assessed if LVHT was present since birth or developed during life-time. However, in one case, LVHT was reported to be absent in a previous echocardiogram, developed *de novo* during TTS, and disappeared after 3 months [45]. In 4 of the 8 patients, follow-up investigations were reported, and in all of them, regression or disappearance of LVHT was observed [38–40, 45]. NMD or psychiatric disorders were reported in 7 of these 8 patients.

6.2 Comments

Unfortunately, our knowledge about the co-incidence of TTS and LVHT is limited to 8 case reports. Thus, the conclusions drawn from these observations are preliminary and can be only hypothesis-generating.

Whether LVHT and TTS are patho-physiologically connected remains unclear. The apical akinesia during TTS may unmask the hypertrabeculated myocardium and increase the probability to detect LVHT.

Additionally, coronary microvascular dysfunction and an impairment of coronary flow reserve have been reported in LVHT-patients [46, 47]. Systolic dysfunction is a frequent finding in LVHT, and it can be assumed that stress may induce a further deterioration of systolic function and TTS. Possibly, catecholamine stress may further deteriorate the pre-existing myocardial impairment in patients with NMD. Possibly, TTS is another, hitherto, not recognized complication of LVHT. In this respect, it is conceivable that already little stress triggers the development of TTS in LVHT. Whether patients with LVHT and a NMD are more prone to develop TTS than LVHT patients without NMD requires further investigations. Additionally, there is a need to clarify, whether cardiomyopathies are generally a predisposing factor for TTS. It can be hypothesized that in a patient with cardiomyopathy, the myocardium is less resistant to catecholamines than the normal myocardium.

Interestingly, 2 of the 8 (25%) patients developed recurrent TTS, which is a high rate. From registries, recurrence of TTS is reported to occur in 7.5% during 5.2 years, 4.7% during 2.5 years, and 4% during 2.2 years [33, 34, 48]. In one of these studies, NMD were identified as predictors for TTS-recurrence [34]. It has to be assessed in larger studies with longer follow-up, if LVHT is a predictor for recurrent TTS.

A further intriguing finding is, that LVHT regressed or disappeared as the left ventricular wall motion improved. This was reported in all 4 of the 8 patients in whom follow-up investigations have been carried out by echocardiography or cMRI, as indicated in Table 4 (Ref. [38–40, 45]). Disappearance or regression of LVHT in adults has been reported in several cases. This phenomenon was observed in association with a decrease in left ventricular size, an improvement of left ventricular systolic function either due to successful pharmacotherapy, cardiac resynchronization therapy, after myocarditis, but also in patients with decreased systolic function [49]. In most reported cases it remains unclear, whether trabeculations in fact regress or are still present, but not more visible because of a decrease in left ventricular size resulting in smaller spaces between the trabeculations. The incidence of disappearance among LVHT patients is currently unknown, including the question whether LVHT with TTS is more prone to disappear than LVHT without TTS.

6.3 Therapeutic implications

Since prospective studies are neither available for patients with TTS nor with LVHT nor with NMD associated with TTS or LVHT, therapy should be carried out, using guidelines for patients with heart failure, when appropriate [23]. This overview of cases with LVHT and TTS indicates that they have a high risk of recurrence. Therefore, in patients with LVHT, cardiologic surveillance with long-term treatment with angiotensin-converting enzyme-inhibitors and beta-blockers, might be useful to prevent its recurrence. Psychiatric disease and NMD should be adequately treated to prevent them from becoming triggers of TTS. NMD patients with LVHT should avoid emotionally and physically stressful situations not to trigger TTS.

7. Conclusions

Cases with LVHT and TTS seem to be frequently associated with NMD and have a high risk of recurrence. LVHT seems to disappear after TTS but it remains unclear whether trabeculations in fact regress or are still present, but not more visible because of a decrease in left ventricular size resulting

in smaller spaces between the trabeculations. Patients with LVHT and TSS require long-term follow up to assess any changes of these abnormalities over time.

Author contributions

CS and JF designed the research study, performed the research and analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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