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Takotsubo syndrome – A close connection to the brain: A prospective study investigating neuropsychiatric traits

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ABSTRACT

Background: Takotsubo syndrome (TTS) is frequently triggered by a stressful event. Overactivation of the sympathetic nervous system has been hypothesized as the underlying mechanism. In a prospective, cross-sectional, single center study we aimed to investigate neuropsychiatric traits in patients with TTS.
Methods: Twenty-six patients with TTS with a median latency of 17.5 months from their index event underwent detailed medical examination, neuropsychologic examination, and Holter-ECG and were screened for psychiatric comorbidities, chronic stress and personality traits with questionnaires.
Results: 38.5% (10/26) of patients suffered from a neurological disease, and 50.0% (13/26) from at least one mental disorder. In 23.1% (6/26) the hospital anxiety scale (HADS–A) was suspicious for an anxiety disorder. There was a high prevalence of left-handedness (19.2%; 5/26). Despite good performance in cognitive testing, 11 patients had an abnormal score in the fatigue severity scale. Recovery of cardiac function was documented, although symptoms in 69.2% of patients persisted. An increase in the root mean square of the successive differences (RMSSD) ($p = 0.01$) was noted on the Holter-ECG.
Conclusion: The study highlights a high prevalence of psychiatric and neurologic comorbidities in patients with TTS, which so far have been under-diagnosed. Future studies will have to show whether these patients might benefit from a combined psychocardiologic rehabilitation.

1. Introduction

Takotsubo syndrome (TTS) or 'broken heart syndrome' is usually triggered by an acute stressful event leading to transient left ventricular dysfunction [1–4]. It has been suggested that stress plays an important role in initiating this disease [5], as it has been demonstrated that stress hormone release, such as that of norepinephrine, is increased in the acute state of TTS [6].

The brain, specifically the limbic system including the amygdala, the hippocampus and the prefrontal cortex, is crucially involved in the stress response to an external stimulus [7]. Obviously, there is a unique interaction between the brain and the heart in TTS [8,9]. However, until now, researchers have mostly focused on the heart and have neglected the emotional centers in the brain.

There is compelling evidence that the brain-heart connection may be critical in understanding the pathophysiology of TTS and needs to

Abbreviations: ESS, Epworth Sleepiness Scale; FPI-R, Freiburg Personality Inventory, revised version; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; HRV, Heart Rate Variability; IA, Interoceptive awareness; MCI, Mild Cognitive Impairment; MoCA, Montreal Cognitive Assessment; RMSSD, Root Mean Square of the Successive Differences; SCSS, Screening Scale for Chronic Stress; SDANN, Standard Deviation of sequential five-minute Normal to Normal means; SDNN, Standard Deviation of Normal to Normal interbeat interval; TICS, Trier Inventory for Chronic Stress; TMT, Trail Making Test; TTS, Takotsubo syndrome; VAS, Visual analog scale.

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be investigated in more depth by a multidisciplinary approach. We propose a relationship between dysfunction in neuronal structures and the susceptibility to TTS and its clinical sequelae. Therefore, the aim of the present study was to investigate, alongside cognitive functioning, also parameters of the autonomic nervous system that are typically mediated by brain structures, comprising limbic system and prefrontal cortex. These sites may arguably be involved in the development of TTS since they are known for their role in stress responses and modulation of the autonomic nervous system [10].

2. Methods

2.1. Study population

Eighty-six patients from the leading hospital University Hospital Zurich of the International Takotsubo Registry (www.takotsubo-registry.com) [4] were screened for the present study. Out of these, 26 patients gave their informed consent to participate in the present study (Fig. 1). The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki as reflected in a priori approval by the local ethics committee, and the fact that all patients gave written informed consent before participation.

Data on preexisting medical history, lifestyle change after the TTS event, other acute stress events and aggravation or first manifestations of health related problems were obtained by medical interview. Patients were asked about their psychosocial background, remarkable biographic events, traumatic life events and psychiatric and neurological comorbidities. The definitions for diagnosed comorbidities are in accordance with the current version of International Classification of Diseases (ICD – 10, version 2010).

2.2. Questionnaires

We investigated the autonomic integrity, psychosocial environment and psychological condition of all patients. The following questionnaires were used: Hospital Anxiety and Depression Scale (HADS) [11], the Epworth Sleepiness Scale (ESS) [12] and the Fatigue Severity Scale (FSS) [13].

Furthermore, two additional psychological self-assessment questionnaires were adopted to quantify chronic stress and to describe personality traits: the Trier Inventory for Chronic Stress (TICS) [14] and the Freiburg Personality Inventory (FPI-R) [15].

2.3. Clinical neurological examination

All patients underwent a comprehensive neurological examination including a focus on dysregulation of the autonomic state. Cranial nerve function, peripheral reflexes and motor functions were assessed. Furthermore, coordinative performance and sensibility were tested by exteroception and proprioception. The neurologic examination was supervised by a board certified and trained specialist (CB).

2.4. Neuropsychological examination

To assess handedness, the Chapman and Chapman inventory was administered to all patients [16]. Deficits in cognitive functioning, i.e. in alertness and concentration, executive functions, memory, speech, visuoconstructive ability, arithmetic ability and orientation were assessed by the Montreal Cognitive Assessment (MoCA) [17]. Figural fluency as a prefrontal executive function was tested with the five-point test [18], assessing predominantly nonverbal, right-hemispheric function. The neuropsychologic testing was supervised by a board certified neuropsychologist (PB).

2.5. Interoceptive awareness

Interoceptive awareness (IA) was tested using the Mental Tracking Method [19]. Participants were instructed to start silently counting the number of heartbeats they perceived during a time interval indicated by the experimenter. The IA task consisted of two sessions, each with four time intervals (100 s, 45 s, 35 s and 25 s), which were presented in random order. Real-time heart beat counting was conducted using the CONTEC CMS-50E finger pulse oximeter and the corresponding analyzing software. The second session was performed after experiencing mild emotional stress induced by Stroop task [20]. Only patients with positive scores were included in the analysis of IA ($n = 25$). A visual analog scale (VAS) ranging from 0 to 10 was used to evaluate experienced emotional stress, with 10 indicating the most intense stress. We used the German version of the Victoria Stroop task with three rounds of increasing level of difficulty (dots, neutral, color) [21]. The investigation of IA was supervised by a board certified specialist (MT).

2.6. Heart rate variability

The impact of the autonomic nervous system on cardiovascular function was assessed by the heart rate variability (HRV) test as described before [22,23]. Two trained cardiologists (FS, AS) analyzed the

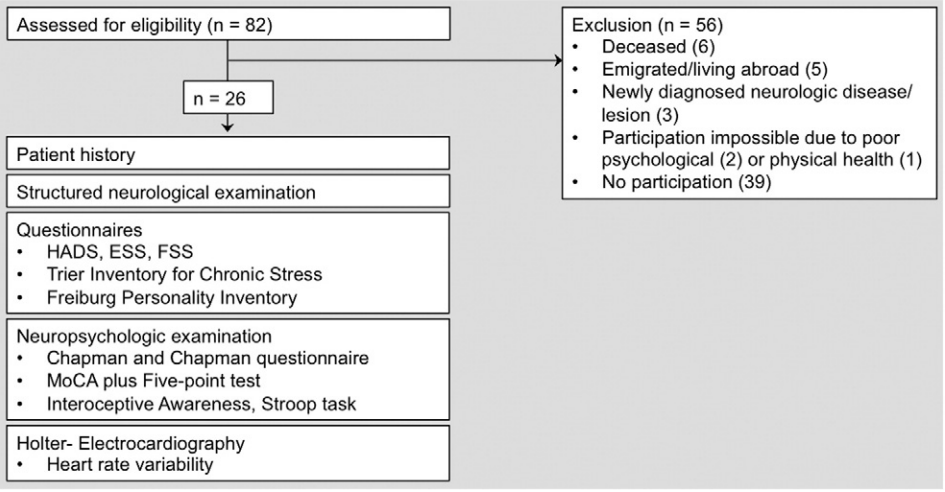

Fig. 1. Study flow chart. Of eighty-two eligible patients with Takotsubo syndrome, 26 patients participated in the present study and underwent assessment of neurologic, neuropsychologic, and autonomic traits. ESS, Epworth Sleepiness Scale, HADS, Hospital Anxiety and Depression Scale, FSS, Fatigue Severity Scale, MoCA, Montreal Cognitive Assessment.