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

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A B S T R A C T

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

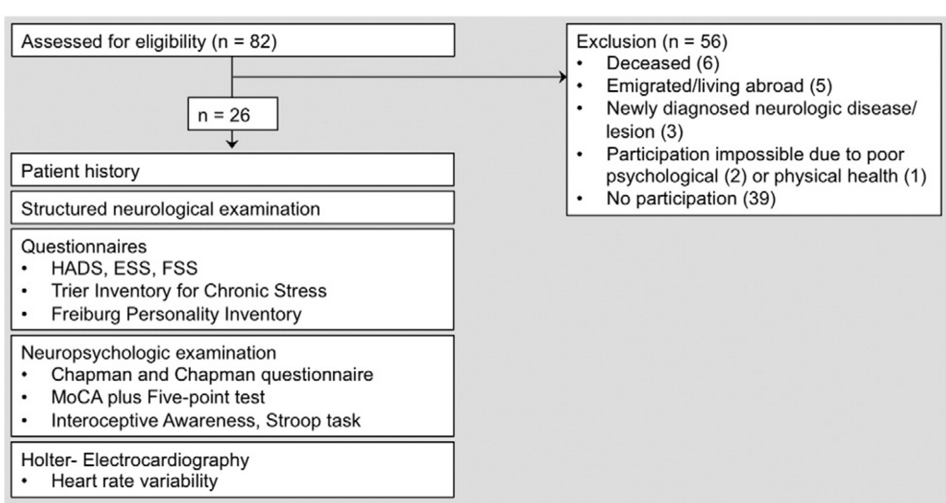

Fig. 1. Study flow chart. Of eighty-two eligible patients with Takotsubo syndrome, 26 patients participated in the present study and underwent assessment of neurologic, neuropsychologic, and autonomic traits. ESS, Epworth Sleepiness Scale, HADS, Hospital Anxiety and Depression Scale, FSS, Fatigue Severity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

Holter-ECGs. HRV parameters were defined according to standard definitions given by the Task Force of the European Society of Cardiology and the National Association for Sport and Physical Education [24] (see Supplementary data).

2.7. Statistical analysis

Descriptive statistics are reported as frequencies and percentages for categorical data. For continuous variables median, mean ± SD and range are given. Correlations were analyzed with Pearson's correlation. Comparisons between patient groups were performed with the Student's T-test in normal distributed data or non-parametrical test (Mann–Whitney U test) if normal distribution was not given. A two-tailed significance level of $p \leq 0.05$ was used. Bonferroni correction was used to control error rate in multiple comparisons. Statistical analysis was performed with SPSS 22.0 (SPSS Inc., Chicago, IL) and Stat view 5.01.

3. Results

3.1. Study population

All 26 patients were Caucasian and female with a mean age of 64.9 years (range 32 to 91 years) at the time of the TTS event. The median time from the TTS event to the time of investigation was 17.5 months (range 1.0 to 72.0). TTS was triggered by an emotional event in 57.7% (15/26) and by a physical stressful situation in 19.2% (5/26) of patients. In 23.1% (6/26) no preceding stressor was noted. Before their TTS index event, 53.8% (14/26) reported a decrease in efficiency in daily productivity and 26.9% (7/26) experienced symptoms of chest pain or dyspnea. 7.7% (2/26) suffered from a recurrent episode of TTS. 80.8% (21/26) were identified as being under chronic psychological pressure. The most frequent complaints regarding neurovegetative function were temperature sensitivity (18/26), indigestion (13/26) and a dry mouth (5/26). No weight loss was documented. History of fainting was present in 38.5% (10/26) of patients, with one patient known for symptomatic orthostatic hypotension. One patient complained of a presyncopal condition during walking or situations of intense mental stress. Interestingly, 69.2% (18/26) reported about emerging symptoms since the TTS episode despite complete cardiac recovery as documented by echocardiography (i.e. effort intolerance, palpitations, stenocardia or dyspnea during mental stress). These symptoms were neither associated with cardiac/non-cardiac comorbidities nor with a major cardiac or cerebrovascular event (data not shown), as evaluated during a clinical visit. Baseline characteristics and clinical course are shown in Table 1.

Table 1
Baseline characteristics.

Age at TTS event (years), mean ± SD (range)	64.9 ± 13.5 (32–91)
Female	26/26 (100.0)
Caucasian	26/26 (100.0)
Anamnestic chronic stress	21/26 (80.8)
Cardiovascular risk factors	
≥3 cardiovascular risk factors	6/26 (23.1)
Arterial hypertension	19/26 (73.1)
Positive family history	12/26 (46.2)
Current or former smoker	9/26 (34.6)
Obesity WHO grade I-III	7/26 (26.9)
Hypercholesterolemia	5/26 (19.2)
Diabetes mellitus Type II	3/26 (11.5)
Cardiovascular history	
Status post TTS event	2/26 (7.7)
Coronary artery disease	5/26 (19.2)
Lifestyle change after TTS	8/26 (30.8)
Cardiac rehabilitation	2/26 (7.7)
Persistent symptoms, any	18/26 (69.2)
Effort-dependent thoracic symptoms*	3/26 (11.5)
Thoracic symptoms during mental stress*	5/26 (19.2)
Dyspnea	4/26 (15.4)
Palpitations*	4/26 (15.4)
Effort intolerance*	9/26 (34.6)

Data are numbers of patients (%) unless otherwise indicated. TTS, Takotsubo syndrome, WHO, World Health Organization.
* Multiple answers possible.

3.2. Psychiatric comorbidities

Mental disorders were found in 57.7% (15/26) of all patients, which had been diagnosed prior to the index event. 69.2% (18/26) suffered from depressive mood, half of whom had been diagnosed with an affective disorder (ICD-10, F30-F39). 3.8% (1/26) suffered from phobia (ICD-10, F40.-) and 7.7% (2/26) had subjectively experienced a panic attack once in their lifetime, but did not seek medical advice. In addition, 7.7% (2/26) had a history of anorexia nervosa (ICD-10, F50.0) and 3.8% (1/26) previously attempted suicide. 7.7% (2/26) had been physically abused in the past.

3.3. Neurological comorbidities

23.1% (6/26) of patients suffered from chronic musculoskeletal pain. Migraine was present in 19.2% (5/26), with epigastric aura in two patients and visual aura in one patient. One patient described the pain as left-dominant. 15.4% (4/26) had insomnia and 7.7% (2/26) suffered from restless legs syndrome. 7.7% (2/26) suffered from epileptic disorder. One patient had symptomatic focal epilepsy with secondary generalization first diagnosed during the TTS event. The second patient suffered from symptomatic complex focal epilepsy and generalized tonic–clonic spells first diagnosed 15 years before the TTS event. Both patients presented with status epilepticus when TTS was diagnosed. In both patients, interictal electroencephalography showed abnormal right-hemispheric discharges in the temporal electrodes and anterior quadrant. As a structural correlate of her epileptic disorder, one patient had two intra-cerebral aneurysmas, one of them located in the right posterior communicating artery and clipped two years prior to TTS event. 7.7% (2/26) of patients had a history of traumatic brain injury, of whom one patient presented with acute TTS accompanied by a contusio cerebri and with an epidural hematoma, treated conservatively. 3.8% (1/26) had suffered from a right hemispheric cerebral hemorrhage with left temporobasal ischemic areas, which was most likely due to a pituitary adenoma. Furthermore, 3.8% (1/26) had cerebrovascular ischemia. A complete list of comorbidities is presented in Table 2.

3.4. Questionnaires

The average HADS-A score was 6.0 ± 3.3 points (0 to 14). In 23.1% (6/26) of patients, scores were suggestive of an anxiety disorder. Out of these, only one patient was diagnosed with an anxiety disorder and received both pharmacological and psychotherapeutic treatment. The average HADS-D score was 4.6 points, SD 3.2 points (range 0 to 11). A diagnosis of a depressive disorder was found in 30.8% (8/26) of the study population. The average ESS score was 5.9 points, SD 2.7 points (range 2 to 13). 11.5% (3/26) had an ESS score of 10 or higher. The average FSS score was 3.4 points, SD 1.6 points (range 0.4 to 6.3). 42.3% (11/26) had a score equal or greater than 4. Patients with recent hospital discharge showed higher scores in FSS, but the difference was not significant ($p = 0.21$). 34.6% (9/26) of patients showed scores above the 97th percentile in the Screening Subscale of Chronic Stress (SCSS) of the TICS as compared to the age-matched normative data. Average scores for each subscale were between the 48th and 54th percentiles of normative data and thus within normal ranges (Fig. A1, Supplementary data). Patients with persistent thoracic tightness during episodes of mental stress since the index TTS event scored significantly

Table 2
Neurologic and psychiatric comorbidities.

Psychiatric comorbidity, any	13/26 (50.0)
Major depression*	8/26 (30.8)
Bipolar disorder*	1/26 (3.8)
Phobia*	1/26 (3.8)
Eating disorder*	2/26 (7.7)
Cognitive impairment*	2/26 (7.7)
Neurologic comorbidity, any	10/26 (38.5)
Chronic headache*	9/26 (34.6)
Migraine*	5/26 (19.2)
Insomnia*	4/26 (15.4)
Restless-legs syndrome*	2/26 (7.7)
Epilepsy*	2/26 (7.7)
Intracranial aneurysm*	2/26 (7.7)
Status post traumatic brain injury*	4/26 (15.4)
Status post intracranial hemorrhage*	1/26 (3.8)
Status post cerebrovascular ischemia*	1/26 (3.8)
Endocrine, any	5/26 (19.2)
Hypothyroidism	4/26 (15.4)
Infertility	1/26 (3.8)
Gastrointestinal, any	3/26 (11.5)
Irritable colon	2/26 (7.7)
Status post gastric-bypass	1/26 (3.8)
Oncologic, any	4/26 (15.4)
Non-small cell lung cancer (NSCLC)	1/26 (3.8)
Status post thyroid carcinoma	1/26 (3.8)
Status post gastrointestinal stroma tumor (GIST)	1/26 (3.8)
Status post ovarial carcinoma	1/26 (3.8)

Data are numbers of patients (%).
* Multiple answers possible.

higher in the subscale of social tension ($p < 0.001$). In the FPI-R, high and low manifestation in the following personality traits were found: life satisfaction (15.4% high, 7.7% low), social orientation (7.7% high, 3.8% low), inhibition (7.7% high, 3.8% low), excitability (11.5% high, 3.8% low), aggressiveness (15.4% high), strain (15.4% high, 11.5% low), somatic distress (3.8%high), health worries (3.8% high, 19.2% low) and openness (15.4% high, 3.8% low). Emotional stability was found to be high in 3.8% (1/26) and low in 7.7% (2/26) of patients (Fig. A2, Supplementary data).

3.5. Neurological examination

Pathological findings were present only in 11.5% (3/26) patients particularly in those with epilepsy or ischemic cerebrovascular disease.

3.6. Neuropsychological examination

19.2% (5/26) patients were left-handed and one patient was ambidextrous. Left-handedness was equally frequent among sub-types of TTS according to contractile pattern (typical versus atypical; $p = 0.08$). Cognitive functioning as established with the MoCA was below the respective age norm in 19.2% (5/26) of patients for the total score. The low scores were found mainly in visuoconstructive (drawing a cube), word-finding (F-word test) and memory tests. The low scores of two patients were due to previously diagnosed cognitive impairments as known sequelae of their epileptic disorders. These patients were excluded from the analysis of neuropsychological tests. Average test scores compared to normative data are depicted in Fig. 2. TTS patients produced fewer 5-point designs than the respective age norms ($p = 0.047$) [25]. The median interference score in the Stroop task, defined as the ratio between time run 3 and time run 1; [26], was significantly lower than that of the age-matched general population ($p = 0.001$) indicating a better-than-normal interference control.

3.7. Interoceptive awareness

There was no significant difference between IA values of run 1 (baseline) and run 2 (mild mental stress induced by the Stroop task; $p = 0.20$). Induction of mild mental stress was reflected by significant heart rate increase during the Stroop task ($p < 0.001$). Average experienced stress measured by VAS scale was 3.6 points, SD 2.5 (range 0–9).

3.8. Heart rate variability

HRV parameters of interest were within expected limits: Standard Deviation of Normal to Normal interbeat interval (SDNN) median 114.0 ms (range 60 to 278), Standard Deviation of sequential five-minute Normal to Normal Means (SDANN) median 103.0 ms (range 55 to 252), root mean square of differences (RMSSD) average 53.0 ms, SD 47.4 (range 20 to 223) [27,28]. However, patients with remaining symptoms after their acute TTS event showed significantly higher values in the time-domain parameter RMSSD compared to patients without residual symptoms ($p = 0.01$). There was no significant correlation between HRV parameters and scores in either subscale of the HADS questionnaire or personality traits (p-values all not significant).

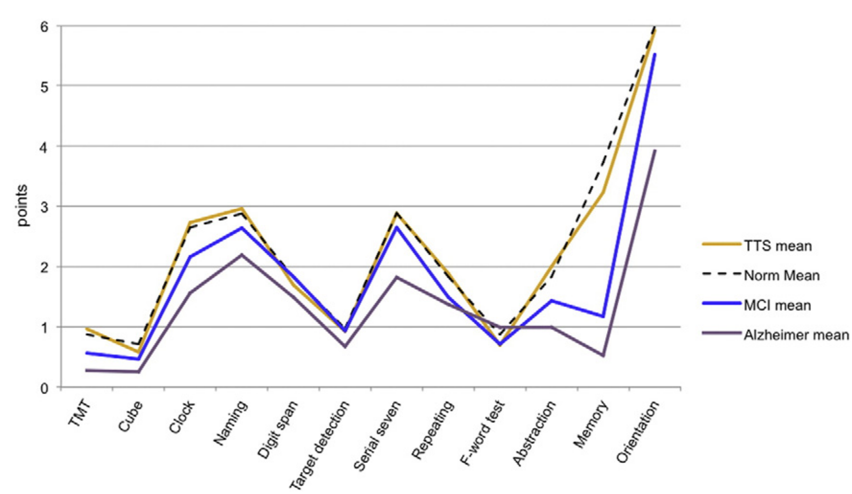

Fig. 2. Neurocognitive test scores in Montreal Cognitive Assessment. Average test scores compared normative data published by Nasreddine et al. [13]. Total scores inferior the respective age norm were found in 19.2% (5/26) of patients. The low scores were found mainly in visuoconstructive (drawing a cube), word-finding (F-word test) and memory tests. TTS, Takotsubo syndrome, MCI, Mild Cognitive Impairment, TMT, Trail Making Test, n = 26.

4. Discussion

The current results provide evidence that patients with TTS suffer from a high prevalence of neurological and psychiatric comorbidities. Interestingly, about a third of the TTS patients showed increased levels of anxiety or/and depression as indicated by high scores in the HADS, suggesting a psychologically distressed state after the occurrence of a TTS event. In addition, about 80% reported experiencing chronic stress, which may have contributed to both cardiac disease and mental disorders [28–30]. However, this finding was not supported by the results of the TICS questionnaire. This might be explained by the delay of the TICS examination. The questionnaire measures experienced stress within three months, while we investigated patients after a median of 17.5 months after the acute TTS event. Most of the patients reported an intensive life style modification after the index event for stress relief, which could have further impact on TICS scores.

The majority of TTS patients reported an emotional or physical trigger event. More than half of the patients reported a decrease in performance or a feeling of an upcoming cold prior to the acute TTS event. We suppose that those symptoms might be due to an imbalance of the autonomic nervous system. However, further investigations are required to explain these findings.

To date, handedness has not been thoroughly investigated in patients with TTS, but previous findings associate a higher risk of cardiac autonomic dysfunction and cardiac arrhythmia with left-handedness [31,32]. Left-handed individuals are generally assumed to comprise 10 to 12% of the general population [33]. In our study population, one fifth of the patients were predominantly left-handed and one patient was ambidextrous. Left-handedness and its associations with cognition seem to be linked to mental disorders such as schizophrenia [34,35] and a low threshold for anxious reactions [36,37]. The relationship of handedness, personality traits and TTS, however, remains unknown.

The statistical time-domain parameters SDNN and SDANN are thought to be acute phase predictors of relatively poor prognoses [28]. Previous studies support our current findings; these time-domain parameters are reduced between the acute phase and the consecutive normalization period of several months [28,38]. As expected, the SDNN and SDANN values were within normal range, suggesting normal sympathetic function [39]. However, patients suffering from persisting symptoms at the time of follow-up showed significantly higher values of RMSSD compared to those without symptoms. This might be due to excessive vagal activation. Data of frequency-domain parameters to support these findings should be evaluated in further studies. Results of time-domain HRV analysis indicate a parasympathetic rather than sympathetic nervous system dysfunction on long-term follow up, which might be related to the cause of the persisting symptoms. Data of frequency-domain parameters to support these findings should be evaluated in further studies.

Our results suggest that the value of physical rehabilitation as currently used for ACS patients appears uncertain for patients with TTS, since endurance training increases vagal tone [40]. This is a desired effect in patients with ACS, but may unfavorably affect the autonomic balance in TTS patients, given that vagal tone is known to be less prominent in patients after myocardial infarction [41]. This finding, however, is inconsistent in TTS patients [28,38,42], so they should be seen regularly and followed up on a long-term basis to plan a personalized rehabilitation program, possibly with a focus on psychological factors, according to their symptoms. Persistent fatigue should also be considered when providing a rehabilitation plan. High scores in FSS, despite normal scores in ESS, indicate fatigue to be due to asthenity rather than sleep propensity. The new onset of fatigue after the TTS event implies that there is an autonomic dysbalance and that it is not due to hypersomnia or disorders of circadian rhythm.

We regard the latency of the follow-up examination as a limitation of our study. Patients were investigated with a median of 17.5 months (range 1.0 to 72.0 months) after the acute TTS event. Furthermore, the neuropsychological examination, including IA, was conducted at different times of the day, having perhaps posed different challenges for different patients, according to an individual's circadian typology [43]. This might have had an impact on performance. Due to the rather limited sample size and cross-sectional study design, test results need to be confirmed in a larger patient population and with longitudinal study designs to investigate neuropsychological state change in evolution of time.

In conclusion, our study suggests psychiatric comorbidities to be under-diagnosed and we therefore propose to specifically screen patients with newly diagnosed TTS for psychiatric diseases. These patients might benefit from combined psychological and cardiac rehabilitation. Since physical training increases vagal tone, advantage of excessive physical training during rehabilitation should be individually assessed. As possible markers we suggest clinical state and HRV. As shown with the IA task, TTS patients seem to be well aware of emotional experiences and the internal visceral and emotional states and therefore might benefit from supportive, mindfulness-based therapies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcme.2016.06.001.

Author contributions

KNM devised the study with JRG, CT, PB and CB, compiled the data, conducted the data analysis and wrote the manuscript with CT, JRG and PB. KNM read and approved the final manuscript.

JRG devised the study, assisted in data analysis, wrote the manuscript with KNM, PB and CT, and read and approved the final manuscript.

CB devised the study, was responsible for the data acquisition and analysis of neurological investigations, and read and approved the final manuscript.

JJ supervised data collection and the analysis of the psychiatric questionnaires, and read and approved the final manuscript.

MT supervised data collection and the analysis of neuropsychologic tests, specifically IA. MT read and approved the final manuscript.

AS supervised data collection and analyzed Holter-ECG data, and read and approved the final manuscript.

FS supervised data collection and analyzed Holter-ECG data, and read and approved the final manuscript.

TFL read and approved the final manuscript.

MJ read and approved the final manuscript.

EK read and approved the final manuscript.

PB devised the study, supervised data collection and analyzed the data of neuropsychological tests, and read and approved the final manuscript.

CT devised the study, wrote the manuscript with KNM JGR and PB, and read and approved the final manuscript.

Conflict of interest

The authors report no conflict of interest.

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