Central Nervous System (CNS) Disease Triggering Takotsubo Syndrome

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Abstract

Takotsubo syndrome (TTS) is usually triggered by psychological or physical stress. One of the many physical sources of stress are central nervous system (CNS) disorders. CNS disorders most frequently triggering TTS include subarachnoid bleeding, epilepsy, ischemic stroke, migraine, and intracerebral bleeding. More rare CNS-triggers of TTS include posterior reversible encephalopathy syndrome (PRES), amyotrophic lateral sclerosis, encephalitis, or traumatic brain or spinal cord injury. TTS triggered by any of the CNS disorders needs to be recognized since adequate treatment of TTS may improve the general outcome from the CNS disorder as well. Neurologists need to be aware of TTS as a complication of specific CNS disorders but TTS may be triggered also by CNS disorders so far not recognised as causes of TTS.

Keywords: Broken heart syndrome; stunned myocardium; Tako-tsubo; central nervous system; bleeding; stroke; seizures

Citation: Finsterer J, Stöllberger C. Central Nervous System (CNS) Disease Triggering Takotsubo Syndrome. International Cardiovascular Forum Journal 2016;5:36-39. DOI: 10.17987/icfj.v5i0.183

Introduction

Central nervous system (CNS) diseases are common triggers of Takotsubo syndrome (TTS).¹,² The exact prevalence of TTS triggered by CNS disease, however, is unknown since many patients with acute or chronic CNS disease do not undergo electrocardiography or echocardiography. Only in case these patients develop clinical manifestations or blood parameters indicative of cardiac disease, the neurologist refers them to the cardiologist and cardiologic investigations are carried out. Even if patients with CNS disease are cardiologically investigated, TTS may be missed or mixed up with myocardial infarction. This is particularly the case if uncommon TTS types are present. Even if TTS was detected, no appropriate follow-up investigations may be carried out. However, follow-up echocardiography is essential since TTS may be subclinical and recovery from TTS may take up to several weeks.³ From a recent review we know that various different CNS diseases may trigger TTS.¹

CNS disorders reported to trigger TTS

CNS disorders most frequently reported in association with TTS are subarachnoid bleeding (SAB), followed by seizures, and ischemic stroke (table 1).¹ More rarely, migraine, intracerebral bleeding, posterior reversible encephalopathy syndrome (PRES), amyotrophic lateral sclerosis (ALS), bacterial, viral, or immune-mediated encephalitis meningitis, or traumatic brain or spinal cord injury (TBI, TSCI) may trigger TTS. Hydrocephalus, subdural hematoma, venous aneurysm, brain tumor, hepatic encephalopathy, or multiple sclerosis (MS) have been only rarely described as triggers of TTS (table 1). CNS disease, which has not been reported so far to trigger TTS include sinus venous thrombosis, dystonia, brain abscess, pituitary adenoma, hereditary spastic paraplegia, or spino-cerebellar ataxia.

Subarachnoid bleeding (SAB)

SAB has been first described to trigger TTS by Donaldson in 2001.¹ Since then an increasing amount of papers has been published which not only confirmed this initial finding but also demonstrated that among all CNS disorders SAB is the one most frequently triggering TTS.¹ More than 50 papers concerning this topic and reporting >300 patients have been published thus far. The close relation between SAB and TTS has been also confirmed in large cohort studies showing that TTS in SAB patients occurs with a frequency of 0.8-33% of the patients.⁵,⁶ The wide range of these figures has been attributed to highly variable frequencies of echocardiographic investigations of SAB patients and by differences of the female-to-male ratio between the studies. In 86% of the cases with SAB-triggered TTS females are affected. Age at occurrence of TTS is highly variable ranging from 24y to 90y. The classical type of TTS was reported in 71% of the cases, the midventricular type in 5%, the inverted type in 22% of the cases, and the global type in a single case. The outcome is fair in almost two thirds of the cases and fatal in one third of the cases. Patients with inverted or midventricular type had a worse outcome as compared to patients with the classical type. In a single patient even global hypokinesia was reported.⁷ SAB
patients with an initially high Hunt-Hess score (HHS) more likely develop TTS than patients with an initially low HHS.\textsuperscript{2,3} Patients taking beta-blockers when experiencing SAB have a lower risk to develop TTS than patients without beta-blockers.\textsuperscript{4} Patients with SAB should generally undergo echocardiography since up to one third of the SAB patients can develop TTS, since TTS can be subclinical, and since the outcome of SAB patients is better if an accompanying TTS is treated than when it remains untreated. Due to the underlying pathology, the outcome in SAB-triggered TTS may be generally worse as compared to TTS triggered by other CNS disorders.

### Seizures

Seizures have been reported to be the CNS disorder second most frequently triggering TTS.\textsuperscript{1} In all patients so far reported complex partial seizures, generalised tonic-clonic seizures or generalised epileptic state preceded the development of TTS.\textsuperscript{11} Most of these reports concern single patients. The largest case series of seizure-triggered TTS included only 5 patients.\textsuperscript{12} No prospective studies have been carried out to assess frequency, age and gender distribution, epidemiology, morphology, treatment, or outcome of seizure-triggered TTS. So far, 74 patients with seizure-triggered TTS have been reported [personal communication]. According to those studies in which age at occurrence had been reported, age ranged between 18 and 82 years. In the majority of the so far reported cases with seizure-triggered TTS, the classical type of TTS was found and only single patients with the midventricular or the inverted type have been published. The outcome was fair in the majority of the cases and only few fatalities have been reported. In a single patient seizure-triggered TTS was complicated by rupture of the left ventricle.\textsuperscript{13} The low number of fatalities challenges the assumption that TTS is one of the causes responsible for sudden unexplained death in epilepsy (SUDEP). Whether seizure type, seizure frequency, or antiepileptic medication influence frequency, epidemiology, clinical presentation, or outcome of seizure-triggered TTS remains speculative.

### Ischemic stroke

Ischemic stroke is the CNS disorder third most frequent CNS disorder triggering TTS.\textsuperscript{1} Ischemic stroke as a trigger of TTS has been reported in 25 papers so far (table 1). Altogether, 33 patients with stroke-triggered TTS were reported in these publications. Ischemic stroke was located supratentorially in the majority of these cases. Only in three cases infratentorial stroke was identified.\textsuperscript{14,15,16} Spinal cord ischemia has been reported in a single patient as a trigger of TTS.\textsuperscript{17} Only two patients had a transitory ischemic attack.\textsuperscript{18,19} Age ranged from 28 to 90 years. Twenty of the patients were female and 4 were male, in 9 patients gender was not reported. The classical type of TTS was found in 25 patients and the inverted type in one patient.\textsuperscript{15} In the remaining cases the TTS type was not reported. The outcome of TTS was favorable in 22 cases, not mentioned in 8 cases, and fatal in 3 cases. In the largest series of 24701 TTS patients so far reported, 655 patients had stroke/TIA as an underlying disease.\textsuperscript{20} Unfortunately, no details were provided, if ischemic stroke in fact triggered TTS in all these patients or if patients had only a history of previous stroke without a causal relation with TTS.\textsuperscript{20}

### Migraine

Migraine or status migrainosus in association with TTS has been reported in 3 studies in altogether 13 patients so far (table 1).\textsuperscript{21,22,23} Thus, migraine is the CNS disorder fourth most frequently triggering TTS. All 13 patients so far reported were female and age at occurrence of TTS ranged from 25 to 48 years.\textsuperscript{1} All 13 patients had developed classical TTS. The outcome was reported only in 2 patients and both made a full recovery.

### Intra-cerebral hemorrhage (ICH)

ICH is the CNS disorder fifth most frequently triggering TTS (table 1).\textsuperscript{1} ICH has been only occasionally reported as a trigger of

### Table 1. CNS disorders triggering TTS

<table>
<thead>
<tr>
<th>CNS disorder</th>
<th>NOP</th>
<th>Sex</th>
<th>AAO</th>
<th>TTS type</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subarachnoid bleeding</td>
<td>312</td>
<td>225f, 36m</td>
<td>24-90</td>
<td>55 classic, 16 inverted</td>
<td>53 FR, 6 IR, 31 fatal</td>
<td>[9]</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>71</td>
<td>46f, 9m</td>
<td>19-83</td>
<td>46 classic</td>
<td>4 FR, 3 fatal</td>
<td>[12]</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>33</td>
<td>20f, 4m</td>
<td>28-90</td>
<td>25 classic, 1 inverted</td>
<td>22 FR, 3 fatal</td>
<td>[14]</td>
</tr>
<tr>
<td>Migraine</td>
<td>13</td>
<td>13f</td>
<td>25-48</td>
<td>13 classic</td>
<td>2 FR</td>
<td>[21]</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>12</td>
<td>9f, 3m</td>
<td>10-94</td>
<td>7 classic</td>
<td>8 FR, 2 fatal</td>
<td>[24,47]</td>
</tr>
<tr>
<td>PRES</td>
<td>10</td>
<td>10f</td>
<td>55-82</td>
<td>9 classic</td>
<td>9 FR</td>
<td>[27,28,29]</td>
</tr>
<tr>
<td>ALS</td>
<td>5</td>
<td>3f, 2m</td>
<td>40-75</td>
<td>5 classic</td>
<td>2 FR, 2 faal</td>
<td>[30]</td>
</tr>
<tr>
<td>Trauma</td>
<td>5</td>
<td>2f, 2m</td>
<td>18-69</td>
<td>3 classic, 1 inverted</td>
<td>4 FR</td>
<td>[36]</td>
</tr>
<tr>
<td>Encephalitis/myelitis</td>
<td>5</td>
<td>3f, 2m</td>
<td>10-65</td>
<td>4 classic, 1 inverted</td>
<td>2 FR, 1IR</td>
<td>[31]</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2</td>
<td>1f</td>
<td>12</td>
<td>2 classic</td>
<td>FR</td>
<td>[42]</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>1</td>
<td>f</td>
<td>54</td>
<td>classic</td>
<td>FR</td>
<td>[45]</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>1</td>
<td>f</td>
<td>48</td>
<td>classic</td>
<td>IR</td>
<td>[40]</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>1</td>
<td>na</td>
<td>na</td>
<td>classic</td>
<td>FR</td>
<td>[41]</td>
</tr>
<tr>
<td>Venous aneurysm</td>
<td>1</td>
<td>m</td>
<td>child</td>
<td>classic</td>
<td>FR</td>
<td>[42]</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
<td>m</td>
<td>26</td>
<td>1 inverted</td>
<td>FR</td>
<td>[46]</td>
</tr>
</tbody>
</table>

Altogether 10 patients have been published in whom ICH triggered TTS. In six patients ICH was located supratentorially and in 4 patients infratentorially. Six patients were female and 4 were males. Age ranged from 23 to 94 years. Seven patients presented with the classical type of TTS and 3 with the inverted type.1 The outcome was reported in 8 patients and fair in 6 patients and fatal in 2.1 In a study of 948 ICH patients, 3.8% had developed acute heart failure without mentioning how many really had TTS.26 Whether patients with rupture into the ventricles and bleedings with space-occupying effect carry a higher risk of developing TTS than patients without is unknown. It is also unknown if intraventricular lysis of the blood clot has a preventing effect with regard to the development of TTS. Rarely, bleeding locating in the spinal cord, such as in a patient with an intraspinal haemorrhage from a perimedullary AV-malformation, may trigger TTS.25

Posterior reversible encephalopathy syndrome (PRES)
PRES is clinically characterized by headache, confusion, nausea, vomiting, seizures, and visual disturbance.27 Cerebral magnetic resonance imaging (MRI) shows multiple cortical and subcortical areas of T2-hyperintensities involving the occipital or parietal lobes bilaterally, or the pons.27 PRES as a trigger of TTS has been reported in ten patients so far.28,29 All ten patients were female. Age at diagnosis ranged between 55 and 82 years. Nine of the patients developed the classical apical type of TTS. In one of them a neurogenic stunned myocardium was described. Nine of the patients made a full recovery, in one patient the outcome was not reported.28,29 Concerning the frequency of PRES among TTS patients, a recent study of 224 TTS patients showed that 2.7% had a history of PRES.28 Whether blood pressure values and extension of the lesions in patients with PRES correlate with the probability of developing TTS, is unknown since no prospective studies are available.

Amyotrophic lateral sclerosis (ALS)
ALS is a sporadic or hereditary motor neuron disease affecting the upper and lower motor neuron or the prefrONTAL cortex. ALS is characterized by progressive weakness, wasting, fasciculations, and spasticity affecting the limb, axial, bulbar, or respiratory muscles. ALS has been reported to trigger TTS in five patients so far.28 Three of these patients were female and two male (table 1). Age ranged between 40 and 75 years (table 1). All 5 patients developed the classical TTS type. According to this study, the most frequent cardiac complication of ALS is TTS.28 Why patients with ALS develop TTS is unclear but most likely it is stress from anxiety. An argument against this assumption, however, is that there are also other conditions in which anxiety occurs without triggering TTS. Stress in ALS could be additionally induced by dysphagia or respiratory dysfunction.

Infectious / immune encephalitis
CNS infectious disease has been reported in 5 publications to trigger TTS.21-25 These 5 publications reported 5 patients of which 3 were female and 2 male. Age ranged from 10 to 73 years. One patient had a methicillin-resistant staphylococcus aureus (MRSA) meningitis,26 one a listeria encephalitis,21 one aseptic encephalitis,26 one aseptic myelitis,21 and one immune encephalitis (limbic encephalitis).24 Four patients presented with the classical type and one with the inverted TTS type. Outcome was reported in four patients. Three patients made a full recovery and one an incomplete recovery.1

Traumatic brain / spinal cord injury (TBI, TSCI)
TBI or TSCI has been only rarely reported to trigger TTS.26-38 Altogether, two patients with spinal cord injury27,28 and two patients with traumatic brain injury36 were reported to have developed TTS after the trauma.26-28 One patient had developed bilateral damage of the dorsal medulla oblongata, resulting in the absence of the baro-reflex.28 Age ranged from 18 to 69 years. Two patients were male and one female and in one case the patient’s sex was not provided. Two presented with classical TTS and one with inverted TTS. In one patient the TTS type was not provided. The outcome was favourable in three patients and in one no information about the outcome was given.

CNS-disorders rarely triggering TTS
Various CNS-disorders have been only occasionally or once reported to trigger TTS. In some of these cases it is even questionable if the CNS-disorder was in fact the trigger or if other circumstances caused the catecholamine storm. CNS-disorders which have been rarely reported as triggers of TTS include mitochondrial disorders,39 subdural haemorrhage,40 removal of a posterior fossa medulloblastoma,41 vein of Galen aneurysmal malformation,42 astrocytoma with hydrocephalus,43,44 hepatic encephalopathy,45 or exacerbation of a multiple sclerosis (MS).46

Discussion
TTS is triggered by physical or psychogenic stress resulting in forced release of catecholamines. Psychogenic stress may be induced by fear, anxiety, surprise, reduced impulse control, or severe depression. Physical stress may result from pain, hypoxia, cardiac arrhythmias, shock, cerebral bleeding, ischemic stroke, seizures, myocardial infarction, heart failure, respiratory insufficiency, or trauma. All patients exposed to severe stress from CNS disease are potential candidates for developing TTS but patients experiencing subarachnoid bleeding, seizures, ischemic stroke, or intracerebral bleeding are particularly prone to develop TTS. These patients should routinely undergo echocardiography if cardiac symptoms develop after the CNS event, if there are ECG dynamics, if creatine-kinase (CK)-elevation or troponin elevation occurs, or if patients present with a myocardial infarction-like appearance. In all patients with CNS disease associated with stress blood myocardial infarction parameters should be determined and a routine ECG should be recorded disregarding if the patient presents with cardiac symptoms or not. CNS-triggered TTS needs to be recognised since adequate treatment may positively influence the overall outcome of these patients. If TTS is adequately treated, the underlying neurological disorder may improve as well. CNS-triggered TTS may gain increasing attention as more CNS disorders will be detected which carry the potential to trigger TTS. The neurologist must be aware of and familiar with TTS not only to differentiate it from myocardial infarction but also to contribute to a favourable outcome of these individuals.

Declarations of Interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”.45

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