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GRAND ROUND
Heart failure

Acute heart and brain failure: a case report

Magdalena Stuetz [1]*, Christian Templin [1], Jelena-Rima Templin-Ghadri[1], Frank Ruschitzka [1], Heiko Pohl [2], and Daniel Hofer[1]

[1]Department of Cardiology, University Heart Center Zurich, University Hospital Zurich, Raemistrasse 100, 8006 Zurich, Switzerland; and [2]Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland

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Background Takotsubo syndrome (TTS) is characterized by often reversible but acute heart failure occurring after an emotional or physical trigger event. The 'brain failure' counterpart is posterior reversible encephalopathy syndrome (PRES) characterized by often reversible but acute neurological symptoms. This case report elaborates on a complex clinical scenario with co-existence of coronary artery disease, TTS and PRES and discusses the pathophysiology, differential diagnosis, and management.

Case summary An 82-year-old woman presented with acute heart failure and generalized tonic-clonic seizures following an acute exacerbation of her chronic back pain. Brain magnetic resonance imaging demonstrated vasogenic oedema consistent with the diagnosis of PRES. Focal wall motion abnormalities on echocardiography without causal coronary stenoses on angiography were consistent with the diagnosis of TTS. After an interdisciplinary approach to differential diagnosis and treatment, the patient was discharged to geriatric rehabilitation without heart failure or neurological defects 4 weeks later.

Discussion TTS and PRES share significant similarities in proposed pathogenesis, epidemiology, management, and clinical outcome. This case report highlights the need for early recognition of this rare association and multidisciplinary approach to diagnosis and treatment as both heart and brain disease may require early intervention up to rapid intensive care support.

Keywords Takotsubo syndrome • Broken heart syndrome • Apical ballooning • Posterior reversible encephalopathy syndrome • Brain heart interaction • Case report

Learning points

- In postmenopausal women with symptoms of acute coronary syndrome or acute heart failure, takotsubo syndrome should always be a differential diagnosis, particularly in cases with concomitant neurologic events or physical/emotional triggers and unexplained clinical findings.
- Takotsubo syndrome and posterior reversible encephalopathy syndrome are associated diseases, which share significant similarities in proposed pathogenesis, epidemiology, and clinical outcome.

Specialties other than cardiology

Emergency medicine, Neurology, Neuroradiology, Intensive care medicine

Introduction

Takotsubo syndrome (TTS) is an acute heart failure syndrome clinically mimicking acute coronary syndrome (ACS).[1,2] TTS

* Corresponding author. Tel: +41 43 25 36260, Email: magdalena.stuetz@usz.ch
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predominantly affects postmenopausal women, ~1–3% of all and 5–6% of female patients presenting with suspected ACS suffer from TTS.[1] Physical or emotional triggers are present in more than 70% of cases and rates of concomitant psychiatric or neurologic disorders are considerably higher in patients with TTS compared to age- and gender-matched patients with ACS.[3] TTS had initially been considered a benign disease, however, different studies have since demonstrated similar rates of severe in-hospital complications to ACS patients, even if treated according to current guidelines.[3,4] The exact pathophysiology of TTS is unknown, but sympathetic stimulation with catecholamine excess seems to have a central role, consecutive impaired microvascular endothelial function is a typical finding in patients with TTS.[1,5,6]

Posterior reversible encephalopathy syndrome (PRES) is characterized by an acute onset of neurological symptoms and vasogenic oedema on brain magnetic resonance imaging (MRI).[7] PRES may affect all age groups but shows a female preponderance.[8] In most cases symptoms and radiologic abnormalities resolve within days to weeks.[9] Pathophysiologically, cerebral hyperperfusion caused by increasing blood pressure is thought to allow for plasma extravasation leading to cerebral oedema, while alternative theories favour endothelial dysfunction with increased vascular permeability caused by endogenous or exogenous toxins.[7–9]

In summary, both TTS and PRES present with acute cardiac or neurological symptoms, share a female preponderance and vascular oedema on imaging, and may resolve spontaneously within days. In this case report, we present a patient suffering from concomitant acute heart failure and neurological symptoms, and discuss differential diagnosis, management, and similarities of TTS and PRES.

Timeline

Time	Progress
1 year prior to the current takotsubo syndrome event	Single-photon emission computed tomography (CT) demonstrated normal left ventricular ejection fraction (LVEF) (83%)
Day 1	
Early in the morning	Heavy back pain
11:00	Generalized tonic-clonic seizure of several minutes
12:00	Admission to the emergency department of a secondary-care hospital: Beside back pain, no discomfort, no pectanginous symptoms Glasgow Coma Scale (GCS) 15, blood pressure 171/91 mmHg, oxygen saturation of 93% on 4 L/min of oxygen, pulmonary oedema, moderate swelling of the lower extremities
12:15	ST-segment elevation in V2–V3 in electrocardiography
13:26	CT showed unspecific cerebellar hypodensity
13:58	Troponin 76 ng/L (normal < 14 ng/L), creatine kinase within normal limits, N-terminal prohormone of brain natriuretic peptide 21 219 ng/L (normal < 738 ng/L)
18:31	Magnetic resonance imaging (MRI) demonstrated vasogenic oedema in the cerebellum, pons, and posterior lobe
Day 4	Transthoracic echocardiography showed an LVEF of 45% with akinesia of the entire apex extending to the midventricular segments
Day 6	
19:38	Transfer to our cardiology ward for left heart catheterization, which was not feasible due to agitation and disorientation of the patient
20:47	Transthoracic echocardiography demonstrated LVEF of 32% with akinesia of the entire apex extending to the midventricular segments of the left and right ventricle (including akinesia of the right free wall) and a moderate to severe low-flow–low-gradient aortic stenosis
Day 13	CT ruled out aortic dissection and pulmonary embolism, but demonstrated new osteoporotic fractures of the thoracic spine
Days 7–18	Intermittent episodes of decreased consciousness, agitation and disorientation, acute renal failure, and electrolyte disturbances
Day 19	Coronary angiography and right coronary artery percutaneous intervention
Day 28	Follow-up echocardiography demonstrated normalized LVEF
Day 36	MRI showed resolution of the vasogenic brain oedema

Case presentation

An 82-year-old woman with a past medical history of valvular heart and coronary artery disease (CAD), stroke, diabetes, atrial fibrillation,

chronic kidney disease, and osteoporosis presented in a secondary-care hospital after a generalized tonic-clonic seizure following an acute exacerbation of her chronic back pain. The patient complained of back pain, but denied chest pain or dyspnoea. On admission elevated blood pressure (171/91 mmHg) was noted, oxygen saturation was 93% on 4 L/min of oxygen and there were signs of biventricular acute heart failure with fine bibasilar crackles indicating pulmonary oedema, elevated jugular venous pressure, and swelling of the lower extremities. A delayed left-sided pupillary response was noted while the neurological status was otherwise unremarkable. The patients long-term medication consisted of apixaban 5 mg b.i.d., lisinopril 20 mg/day, torasemide 30 mg/day, levothyroxine 100 µg/day, acetaminophen 4 g/day, metamizole 3 g/day, fentanyl patch 50 µg/24h, and amitriptyline 25 mg/day. Electrocardiography (ECG) documented sinus rhythm with intermittent ST-segment elevation in the precordial leads (*Figure 1*). Laboratory tests revealed a markedly increased N-terminal prohormone of brain natriuretic peptide (at admission: 21 219 ng/L, max. 59 475 ng/L, normal <738 ng/L) and only modestly elevated troponin values (at admission 76 ng/L, max. 204 ng/L, normal <14 ng/L), while creatine kinase repetitively remained normal. Brain MRI demonstrated bilateral cerebellar and occipital vasogenic oedema (*Figure 2*) consistent with PRES. Echocardiography demonstrated a newly reduced left ventricular ejection fraction (LVEF) with apical akinesia and the patient was transferred to our hospital for left heart catheterization.

Immediate left heart catheterization was planned but initially not feasible due to agitation and disorientation of the patient. Transthoracic echocardiography in our hospital showed a normally configurated left ventricle with a severely reduced biventricular ejection fraction with akinesia of the entire apex extending to the midventricular segments as well as akinesia of the right free wall and a moderate to severe low-flow–low-gradient aortic stenosis (Supplementary material online, *Videos S1–S3*). Computed tomography (CT) ruled out aortic dissection and pulmonary embolism but demonstrated new osteoporotic fractures of the thoracic spine. Concomitant CT angiography demonstrated high-grade diffuse arteriosclerosis and a stented right coronary artery (RCA) with preserved flow in all distal coronary arteries, rendering reliable quantification of coronary stenosis inconclusive. Invasive coronary angiography revealed serial 90% stenoses in the mid-segment of the left circumflex artery (LCX) and a proximal 80% in-stent restenosis in the previously stented RCA (*Figure 3* and Supplementary material online, *Videos S4 and S5*). The left anterior descending artery (LAD) itself demonstrated no significant lesions. Left ventriculography was not conducted due to previously performed echocardiography and acute on chronic renal failure. The RCA was treated with a drug-eluting stent (Supplementary material online, *Video S6*), the stenoses in the LCX were not treated simultaneously because of increased agitation of the patient, which was considered acceptable due to small vessel size, sufficient collateral flow, and lack of angina. Follow-up ECG showed new biphasic T-wave inversions in the precordial leads and QTc prolongation (*Figure 4*), while laboratory tests demonstrated no signs of increasing troponin leakage. Given the

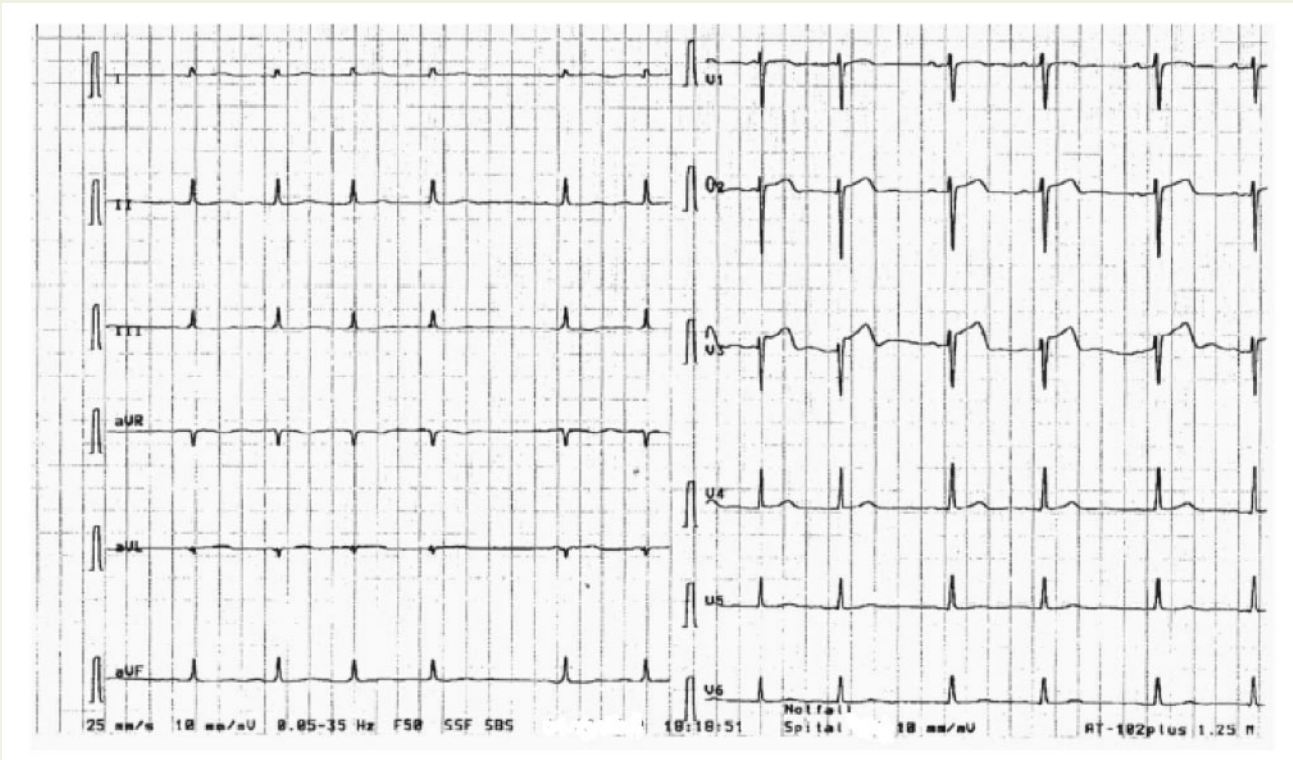

Figure 1 Initial electrocardiography showing sinus rhythm and ST-segment elevation in V2–V3.

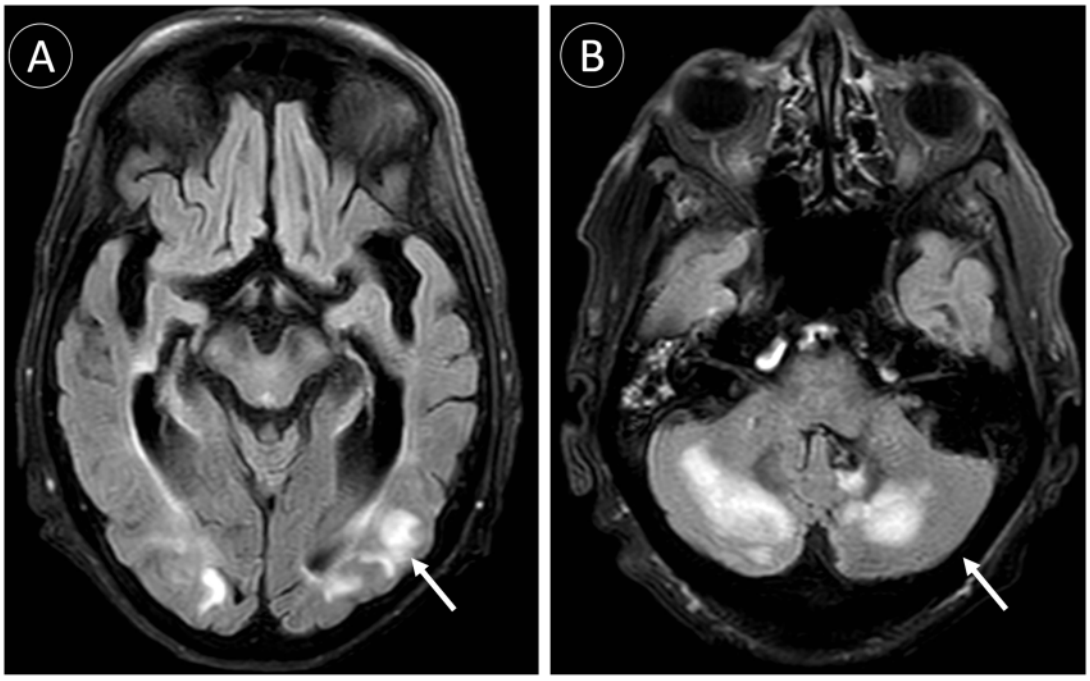

Figure 2 Brain magnetic resonance imaging (T2 weighted). (*A*) The arrow indicates vasogenic oedema in the posterior cerebral lobe. (*B*) The arrow indicates vasogenic oedema in the cerebellum.

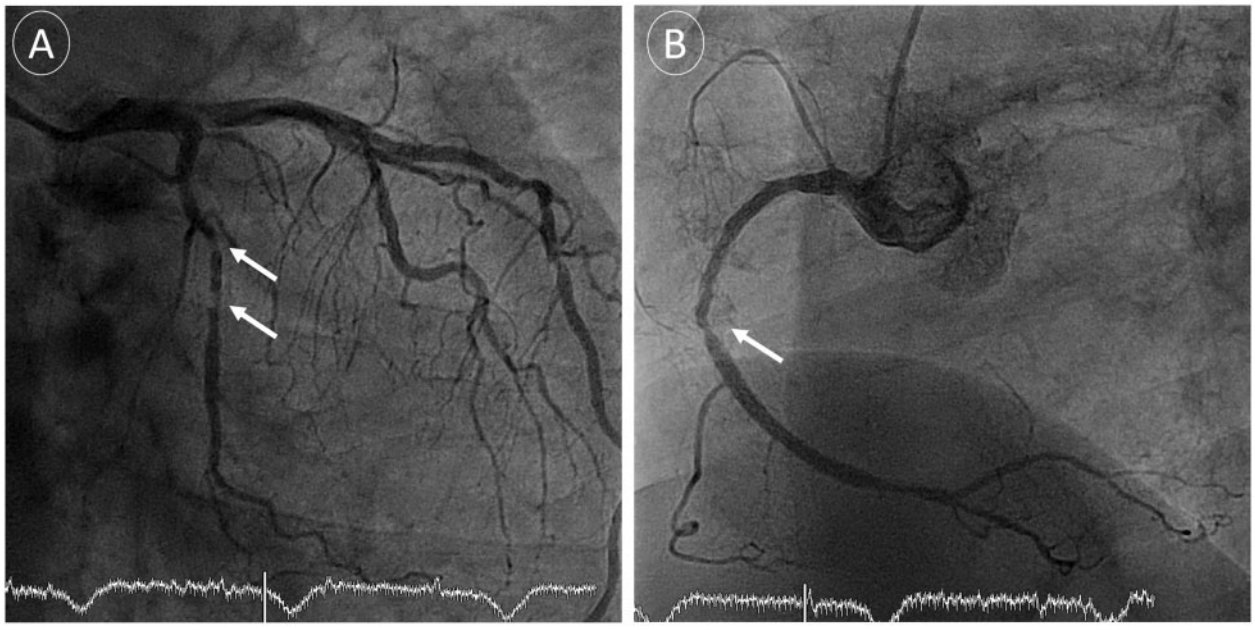

Figure 3 Coronary angiography. (*A*) The arrows indicate a serial 90% stenosis in the left circumflex artery. (*B*) The arrow indicates an 80% proximal in-stent stenosis in the right coronary artery.

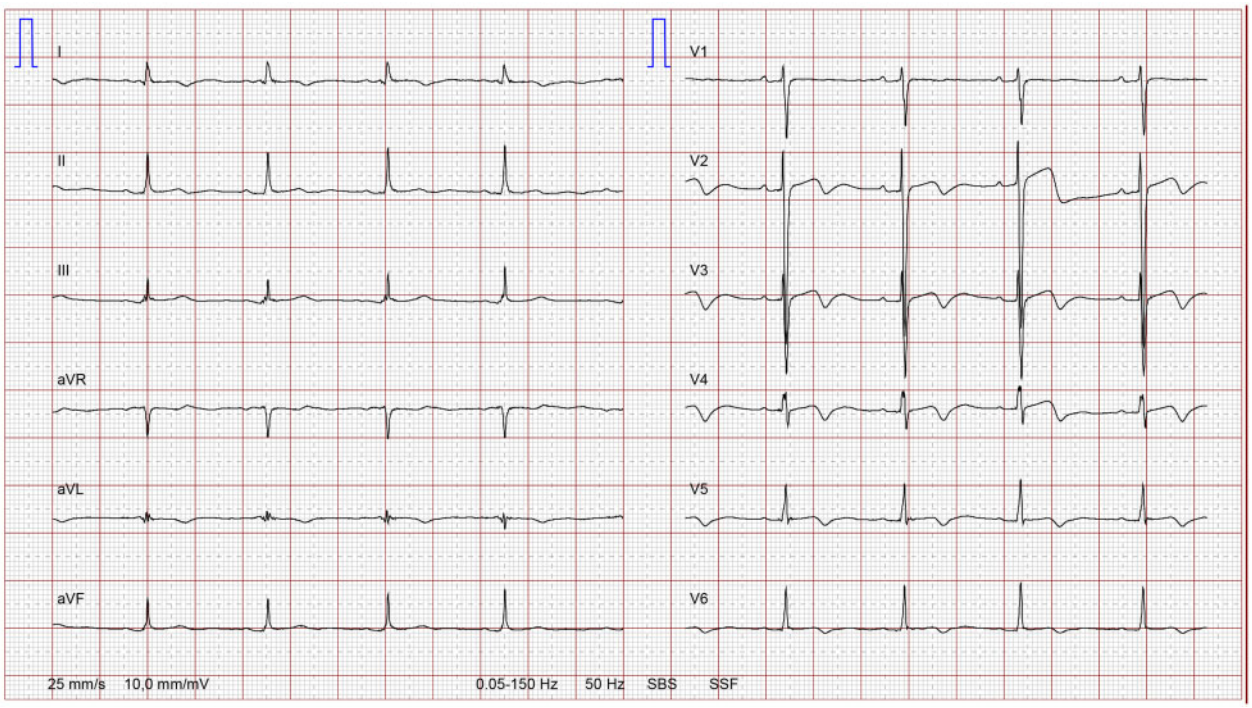

Figure 4 Electrocardiography showing T-wave inversions in I and aVL, biphasic T-wave inversions in V2–V6, and QTc prolongation on Day 13.

Table 1 International Takotsubo Diagnostic Criteria have been developed and published in 2018 by Ghadri *et al*[1]. Compared to previous criteria they take into account that coronary artery disease is not a contradiction in TTS. In our case all diagnostic criteria for TTS were met

1. Patients show transient[a] left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS)[b]
2. An emotional, physical, or combined trigger can precede the TTS event, but this is not obligatory
3. Neurologic disorders (e.g. subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for TTS
4. New ECG abnormalities are ent (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common
6. Significant coronary artery disease is not a contradiction in TTS
7. Patients have no evidence of infectious myocarditis[b]
8. Postmenopausal women are predominantly affected

[a]Wall motion abnormalities may remain for a prolonged period of time or documentation of recovery may not be possible. For example, death before evidence of recovery is captured.
[b]Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of TTS.
Reprinted with permission of Ghadri *et al*[1].

characteristic wall motion pattern with apical ballooning with reduced LVEF and a coronary pathology not explaining the wall motion abnormality in context with ST-segment elevation and prolonged QTc with subsequent T-wave inversion, TTS with concomitant obstructive CAD and PRES was considered as the most appropriate diagnosis and the initial back pain exacerbation due to fractures in the thoracic spine appeared a likely trigger for the TTS event (Table 1).

The patient was treated with analgesia to minimize recurrent triggers (acetaminophen 4 g/day, metamizole 3 g/day, hydromorphone max. 32 mg/day), levetiracetam 1000 mg/day to prevent recurrent seizures, dual antiplatelet medication (aspirin 100 mg/day, clopidogrel 75 mg/day) after coronary artery stenting and intensive heart failure therapy including angiotensin-converting enzyme inhibitors (lisinopril 2.5–10 mg/day, dose was limited by symptomatic hypotension and acute on chronic renal failure) and loop diuretics (varying doses of furosemide IV, max. 70 mg/days or torasemide oral, max. 50 mg/days). Because of bradycardia and hypotension, beta-blockers were postponed. Since the patient refused cardiopulmonary resuscitation, heart rhythm monitoring was not performed despite QTc prolongation.

While heart failure symptoms improved, the clinical course was complicated by intermittent episodes of decreased consciousness, acute renal failure, and electrolyte disturbances. Electroencephalography demonstrated no evidence of epileptic potentials and CT ruled out intracranial haemorrhage, hence we suspected either prolonged PRES symptoms or hypoactive delirium and installed continuous observation and conservative anti-delirious measures. Follow-up cerebral MRI 5 weeks later showed resolution of the vasogenic brain oedema. Follow-up echocardiography 4 weeks later demonstrated complete normalization of LVEF without any residual wall motion abnormalities (Supplementary material online, *Videos S7–S9*).

The patient was discharged 4 weeks after hospital admission without evidence of heart failure and without clinically apparent neurological defects to geriatric rehabilitation. The discharge medication included ramipril 1.25 mg/day for TTS, aspirin 100 mg/day and clopidogrel 75 mg/day after percutaneous coronary intervention on top of edoxaban 30 mg/day for atrial fibrillation, pantoprazole 40 mg/day, torasemide 2.5 mg/day, levothyroxine 100 µg/day, and acetaminophen 4 g/day plus buprenorphine patch 35 µg/24 h for chronic back pain. Levetiracetam was stopped after resolution of vasogenic oedema on cerebral MRI. Regular check-ups for adaption of lisinopril, torasemide, and edoxaban at the patient's general practitioner were planned, as well as cardiologic and neurologic follow-up after 3 months at an outpatient clinic.

Discussion

This case report illustrates challenges in diagnostic and management strategies in patients with TTS and concomitant CAD, as well as a potential association of TTS with patients suffering from PRES.

Acute systolic heart failure with troponin elevation and electrocardiographic alterations may be caused by several causal diseases, of which ACS, TTS, and myocarditis are often primarily considered. If TTS is suspected, the InterTAK diagnostic score can be used to estimate probability of TTS using clinical criteria,[10] which resulted in a InterTAK score >50 for our patient, making TTS highly likely. Concerning further diagnostic strategies, coronary angiography and left ventriculography are considered the gold standard to confirm TTS and rule out ACS.[1] But the diagnosis of CAD by invasive angiography is not at all a contradiction to TTS as these diseases often coexist, rendering differential diagnosis and interpretation of stenoses on invasive angiograms difficult.[1] In acute critical conditions, coronary CT angiography may be considered to rule out progression of CAD, but it may be of limited value in diffuse arteriosclerosis or previously stented coronary arteries, similar to our patient.[4] Cardiac MRI can differentiate between TTS, ACS, and myocarditis, but is often not feasible in patients with concomitant neurological conditions (PRES in our example) or critical medical state.[11] Myocarditis was a differential diagnosis in our patient, but neither a recent infection in the patient's history nor a pericardial effusion or laboratory signs of inflammation were noted.

Since CT angiography could not exclude progression of CAD and MRI was not feasible in our patient, we performed invasive angiography, where the patient received percutaneous intervention of the 80% in-stent restenosis in the proximal RCA. The latter seems inappropriate in retrospect, since biventricular wall motion abnormalities were not consistent with observed coronary lesions and electrocardiographic changes did not match the invasively documented stenoses, while the InterTAK score strongly favoured TTS and dual antiplatelet therapy after coronary intervention is associated with an excess in bleeding risk. On the other hand, we were faced with the differential diagnosis of a concomitant ACS, the patient had known CAD, the RCA was a dominant vessel with a proximal high-grade stenosis that had previously been stented, there was akinesia of the right free wall on echocardiography and we could not rule out overlap of ischaemic and TTS-related wall motion abnormalities. In this complex situation and even after individual risk stratification, the benefit of pragmatic revascularization may be equally counterbalanced by the associated bleeding risk. After discussing the situation with the patient, who primarily wanted to avoid a second coronary angiography in the near future, we decided for revascularization based on the patient's preference. Since wall motion abnormalities with apical ballooning extended above the coronary pathologies, high InterTAK score was identified and T-wave inversions as well as QTc prolongation after invasive angiography was noted, we, however, diagnosed TTS as the most unifying diagnosis, with bystanding CAD.

Even though QTc prolongation is associated with acute neurological events, to the best of our knowledge no association of QTc prolongation and PRES has been reported. T-wave inversions after intermittent ST-elevation can be a sign of reperfusion after thrombotic or vasospastic ACS, but coronary angiography demonstrated no lesions in the LAD and we would have expected a spontaneous reperfusion of a transient thrombotic or vasospastic occlusion to present more acutely.

This case emphasizes that diagnosis of TTS may be challenging in the setting of concomitant CAD and that the decision to treat high-grade stenosis of CAD with concomitant TTS may rely primarily on individual risk stratification, since both over- and undertreatment of CAD is possible in this situation.

Concerning the association of TTS and PRES, we presented a patient with both TTS and concomitant PRES following acute exacerbation of chronic back pain. Both disorders affect predominantly women and are usually reversible with supportive management, but can be life-threatening in the acute phase.[1,3,4] For TTS, angiotensin-converting enzyme inhibitors are indicated as conservative heart failure therapy and have been associated with improved survival and recovery of left ventricular function.[3]Beta-blockers also seem to be reasonable until full recovery of LVEF, although no survival benefit has been demonstrated.[4] QT prolongation is a known substrate for

ventricular arrhythmia, therefore QT-interval prolonging drugs should be avoided and rhythm monitoring is warranted.[4] For PRES, the management of the underlying disease, blood pressure control, and symptomatic control of neurological defects are the mainstay of current treatment strategies.[7,9]

Endothelial dysfunction, caused by excessive catecholamine release and inflammation, has been proposed in both disorders as the potential underlying mechanism.[1,7] In this context, the association of hypertensive episodes with PRES may merely be a bystander of catecholamine-induced high blood pressure. Supporting the pathophysiological relevance of endothelial dysfunction, vasogenic cerebral oedema on MRI is characteristic of PRES[7] while myocardial oedema is a typical finding on cardiac MRI in TTS.[11] A possible association or link of the two syndromes has previously been reported: in one study, 6 out of 224 patients (2.7%) with TTS were also diagnosed with PRES.[2] Reviewing data on PubMed, we identified another 8 case reports of associated PRES and TTS, resulting in a total of 14 patients.[2,12–19] Similar to our case, 13 of these 14 patients were female with an age range of 45–83 years[2,12–16,18,19] and 6 patients developed symptoms of TTS and PRES on the same day,[2,15–17,19] while 3 patients suffered from TTS first,[2] favouring the theory of a common pathogenesis over PRES triggering TTS.

Also similar to our case, a physical or emotional trigger was observed in 12 out of 14 patients.[2,12,14–16,18,19] An autoimmune disease as a potential trigger for endothelial dysfunction was present in seven patients and three had previously been treated with steroids.[2,12] The latter might serve as a trigger for TTS and PRES, since steroid-induced arterial hypertension is thought to be partially mediated by increased vascular sensitivity to adrenergic agonists.[20] One patient suffered from a drug-induced PRES and TTS due to the tyrosine-kinase inhibitor lenvatinib. The pathogenesis was suspected to be mediated by antagonism to vascular endothelial growth factor reducing nitric oxide through inhibition of nitric oxide synthase, which may cause an increased response to catecholamines in some organs.[18]

In conclusion, while it is reasonable to suggest a common causal mechanism, the pathophysiological connection of PRES and TTS is still unclear, but endothelial dysfunction seems to play a major role in both diseases. Patients with concomitant TTS and PRES seem to exhibit a female preponderance, an advanced age and often identifiable physical or emotional triggers.

Conclusion

TTS and PRES share significant similarities in proposed pathogenesis, epidemiology, management, and clinical outcome.

The diagnosis of TTS itself may be challenging, since the clinical phenotype may closely resemble ACS and both conditions may coexist. Therefore, in postmenopausal women with symptoms of ACS or acute heart failure, TTS should always be a differential diagnosis, particularly in cases with concomitant neurologic events or physical/emotional triggers.

In the setting of new heart failure in patients with PRES, TTS should be suspected—likewise, in the case of new neurological symptoms in patients with TTS, PRES should be considered as a potential diagnosis. However, in cases of co-existence of CAD and TTS there is a potential risk for both over- and undertreatment of CAD vs. TTS and management needs to be guided by individual risk stratification and patient preference.

This case report highlights the need for an early recognition of these diseases and a multidisciplinary approach to diagnosis and treatment as both heart and brain disease may require early diagnosis, appropriate intervention, and prompt intensive care support.

Lead author biography

Magdalena Stuetz, MD, graduated from the Medical University of Vienna in 2011. She achieved the board certification in Internal Medicine in 2019 in Switzerland and is now a resident at the Department of Cardiology, University Hospital of Zurich.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: D.H. reports educational grants, speaker fees or fellowship support from Abbott (SJM), Medtronic, Biotronik, Boston Scientific, Biosense Webster, Novartis, and Bayer. C.T. reports collaboration with Biosensors, Abbott Vascular, Boston Scientific, and Schnell Medical. F.R. reports collaboration with SJM/Abbott, Servier, Zoll, Astra Zeneca, Sanofi, Novartis, Amgen, and BMS. All other authors declared no conflict of interest.

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