ESC European Society of Cardiology
European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytab011

CASE REPORT
Other

Case report of Takotsubo syndrome following seizures in a patient with pyruvate carboxylase deficiency

Nikhil Sahdev *, Onyedikachi Oji, Aswin Babu , and Smita Dutta Roy

Cardiology Department, Homerton University Hospital, Homerton Row, Clapton, London E9 6SR, UK

Received 23 August 2020; first decision 15 September 2020; accepted 7 January 2021

Background Takotsubo syndrome (TS) is defined as transient left ventricular dysfunction, which is often related to an emotional or physically stressful event. We describe a case of TS in a lady with pyruvate carboxylase deficiency (PCD). Pyruvate carboxylase deficiency is rare condition with the majority of those affected demonstrating signs of failure to thrive, recurrent seizures, and metabolic acidosis. To our knowledge, this is the first documented case of TS in an individual with PCD.

Case summary This 28-year-old female presented to the emergency department after a tonic-clonic seizure. For 4 days prior to the presentation, she had been suffering from cough and pyrexia. On Day 2, she developed abdominal pain associated with tachycardia and hypotension, and an elevated troponin (791 ng/L). The echocardiogram showed a severely impaired left ventricular systolic function, regional wall motion abnormalities (RWMAs), and a visually estimated left ventricular ejection fraction of 25–30%. Eight days following admission her clinical state significantly improved, with a reduction troponin to 60 ng/L. A repeat echocardiogram on Day 9 showed complete resolution of cardiac function with no RWMAs. Following this, she was discharged from hospital the next day with a diagnosis of TS.

Discussion This is the first case report of TS in a patient with PCD. In this case, multiple aetiologies of TS such as emotional and physical stress, seizures, and acute infection were considered. This case also highlights that TS should be an important differential diagnosis in patients presenting with cardiac symptoms.

Keywords Case report • Takotsubo • Pyruvate • Carboxylase • Seizures

Learning points

- It is important to consider Takotsubo syndrome as a differential in patients who present with cardiac symptoms after seizures.
- Takotsubo syndrome has multiple precipitating aetiologies including physical and emotional stress, acute infection, and seizures.
- Takotsubo syndrome should be considered in patients with pyruvate carboxylase deficiency with cardiac presentations.

* Corresponding author. Tel: 020 8510 5555, Email: Nikhil.sahdev@nhs.net
Handling Editor: Yuichi Tamura
Peer-reviewers: Luca Moderato and Luca Arcari
Compliance Editor: Carlos Minguito Carazo
Supplementary Material Editor: Ayse Djahit

Introduction

Takotsubo syndrome (TS) is defined as transient left ventricular dysfunction, which is often related to an emotional or physically stressful event.[1] Typically, there is left ventricular (LV) regional wall motion abnormalities (RWMAs), which extend past the territory of a single coronary artery.[2] The first case of TS was described in Japan in 1990, where the apical ballooning of the left ventricle resembled a Japanese pot 'tako-tusbo' which was used to catch octopi.[3] Since 1990, the number of diagnosed cases of TS has increased, most probably due to the increased awareness of this condition amongst clinicians. Recent studies suggest that ~2% of ST-elevation myocardial infarction cases can be attributed to TS.[4]

In this case report, we describe a case of TS in a young lady with pyruvate carboxylase deficiency (PCD). Pyruvate carboxylase deficiency is an extremely rare autosomal recessive condition with an estimated incidence of 1 in 250 000.[5] Most individuals affected by the condition show signs of failure to thrive, recurrent seizures, and metabolic acidosis. To our knowledge, this is the first case of TS in a patient with PCD.

Timeline

Day	Department	Events
Day 0	Emergency department	Admitted following an episode of tonic-clonic seizure. pH: 7.11 Lactate: 12.6 mmol/L
Day 1	Acute Medical Ward	Escalated to intensive care unit for glucose and sodium bicarbonate infusions that evening
Day 2	Intensive care unit	Progressively worsening abdominal pain, hypotension, tachycardia, and hyperlactataemia Computed tomography: Bilateral basal peripheral ground-glass opacification. Appearances are suspicious for SARS-CoV-19 pneumonitis. Repeat SARS-CoV-19 swab negative High degree of clinical suspicion and therefore dexamethasone started for treatment of SARS-CoV-19 Troponin: 790 ng/L
Day 3	Intensive care unit	Echocardiogram: Overall severely impaired LV systolic function [regional wall motion abnormality (RWMA) detected mid, distal, and apex]. Apex is akinetic/severely hypokinetic. Visually estimated left ventricular ejection fraction (LVEF) ~25–30% (previously normal echo) Electrocardiogram (ECG): ECG showing RAD, Poor R-wave progression, and QTc-470 ms Troponin: 220 ng/L Treated for acute coronary syndrome (with dual antiplatelet therapy) and heart failure
Day 7	Intensive care unit	Troponin: 60 ng/L Clinically well Stepped down to ward
Day 9	General Medical Ward	Echo: No RWMA and LVEF 50–55% Diagnosis: Takotsubo syndrome
Day 10	Ward	Discharged home

Case presentation

This 28-year-old female presented to the emergency department (ED) after a witnessed tonic-clonic seizure, which was terminated by 10 mg of buccal midazolam. Prior to the seizure, she had been unwell for 4 days with a cough and a high-grade pyrexia reported as 38.5°C.

The patient has a background of PCD, an extremely rare condition that causes lactic acidosis and seizures. Her baseline lactate level is around 4 mmol/L (0.4–0.8 mmol/L), and her last seizures were in 2013 and in 1997. She was not on regular anti-epileptic medication. In addition, she was known to suffer from generalized hypotonia and learning difficulties. In 1998, she underwent an atrial thrombectomy related to central line sepsis with *Candida albicans* species.

On presentation to the ED, her observations were RR-16, HR 72, Saturations 96%, BP 130/72, temperature 37.2°C. Initial physical examination of the cardiovascular, respiratory, and gastrointestinal systems revealed no abnormalities. Blood tests on admission showed no evidence of infection, but a blood gas revealed an acidaemia and hyperlactataemia: pH 7.11 (7.35–7.45), Lactate 11.5 mmol/L (0.4–0.8 mmol/L), BE -20.8 mmol/L (-2 - 3mmol/L) and $HCO3^-$ 8.5 mmol/L (22.0–29.0 mmol/L).

A deficiency of pyruvate decarboxylase results in decreased production of glucose and a reduction in energy production from the mitochondria. Incomplete respiration also results in the accumulation of inorganic acids, which causes metabolic acidosis. Therefore, when the body is under stress (e.g. an underlying infection) patients with PCD are unable to meet their energy demands.

After seeking specialist advice, the patient was treated with 2 mL/kg/h of 10% dextrose to meet her energy demands as patients with PCD often have a decreased glucose production.

The metabolic acidosis was managed with 10 mL of oral sodium bicarbonate 8.4% three times a day. Despite optimal ward-based management, she was admitted to the intensive care unit (ICU) due to her abnormal biochemistry. On ICU, her metabolic acidosis was managed with intravenous 1.26% sodium bicarbonate infusions until her acidosis and base excess had resolved.

On Day 2 in ICU, the patient-reported abdominal pain associated with tachycardia and hypotension. Her computed tomography (CT) abdomen demonstrated no acute intra-abdominal pathology but showed bilateral basal peripheral ground-glass opacification in the lungs; appearances suspicious for SARS-CoV-19 pneumonitis. In addition to the nasopharyngeal swab for RT–PCR detection of SARS-CoV-19 sent on admission, a repeat swab was sent, but both were negative. However, due to a high clinical suspicion with the typical CT changes of bilateral basal peripheral ground-glass opacification, she was treated as having SARS-CoV-19 pneumonitis and was started on 6 mg dexamethasone for 10 days.

A troponin done at the time of haemodynamic instability was raised at 791 ng/L (0–10 ng/L) (6 ng/L on admission). As well as this, a transthoracic echocardiogram showed a severely impaired LV systolic function with RWMAs detected in the mid, distal, and apical regions; and an LV ejection fraction reported as 25–30% (*Figure 1* and *Video 1*). Her electrocardiogram (ECG) showed sinus rhythm with right axis deviation, poor R wave progression, QTc prolongation (470 ms), and T-wave inversion in the precordial leads, leads I and aVL (*Figure 2*). Her previous echocardiogram and ECG performed in 2019 had both been normal. She was started on heart failure treatment consisting of beta-blockade, angiotensin-converting enzyme inhibition as well as dual antiplatelet therapy. Anticoagulation with treatment dose low molecular weight heparin was started based on the history of previous cardiac thrombus and severe hypokinesis on the echocardiogram. In view of the echocardiogram findings, dynamic troponin, and ECG changes she was kept on dual antiplatelet therapy until further investigations were performed.

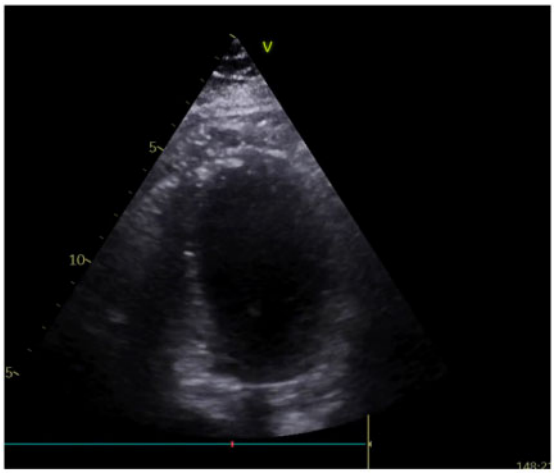
Four days after the initial rise in troponin, there was a significant clinical and biochemical improvement, with a reduction of the troponin to 60 ng/L (0–10 ng/L), hence she was stepped down to a general medical ward. She was due to have a cardiac MRI to further investigate the cause of her cardiac dysfunction, but she did not tolerate this procedure. However, a repeat echocardiogram performed 7 days after her initial troponin rise showed a completely normal cardiac function with no RWMAs (*Figure 3* and *Video 2*). Following this, she was discharged the next day.

The patient was followed up in clinic at 2 and 6 months. On both occasions, she did not suffer from any chest pain, shortness of breath, dizziness, or any further seizures. She also had an echocardiogram that showed normal LV cavity size and LVEF of 60–65% visually.

Discussion

To our knowledge, this is the first case of a patient with PCD presenting with TS. Our patient met a minimum of five out of the seven diagnostic criteria for TS, including transient LV RWMA beyond a single coronary distribution, raised troponin, and ECG changes.[6] Ideally, a coronary angiogram or CT scan would have been useful to rule out coronary artery disease, but the patient was unable to tolerate these investigations. However, the young age of the patient and clinical evolution does not suggest the presence of any culprit coronary artery disease.

Takotsubo syndrome is thought to occur due to a surge in plasma catecholamine levels at over 30 times the normal resting level.[7] In our patient, it is likely that this catecholamine surge is secondary to either her seizures, underlying infection, stressful events, or a combination of all three (*Figure 4*).



Video 1 Clip showing echocardiogram on day 2 of admission – the echocardiogram showed a severely impaired LV systolic function, regional wall motion abnormalities (RWMAs) and a visually estimated LVEF of 25-30%.

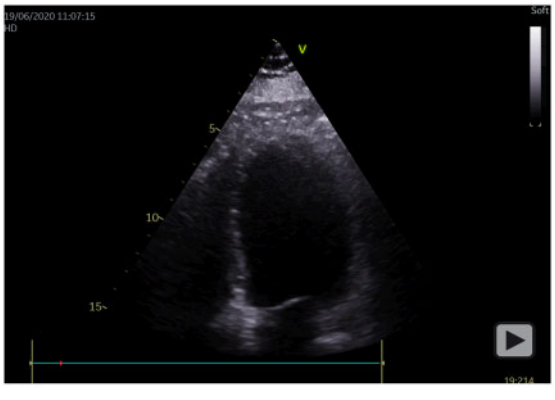


Figure 1 Echocardiogram conducted at the time of clinical instability. Severely impaired left ventricular systolic function with regional wall motion abnormalities detected in the mid, distal, and apical regions; and a left ventricular ejection fraction reported as 25–30%.

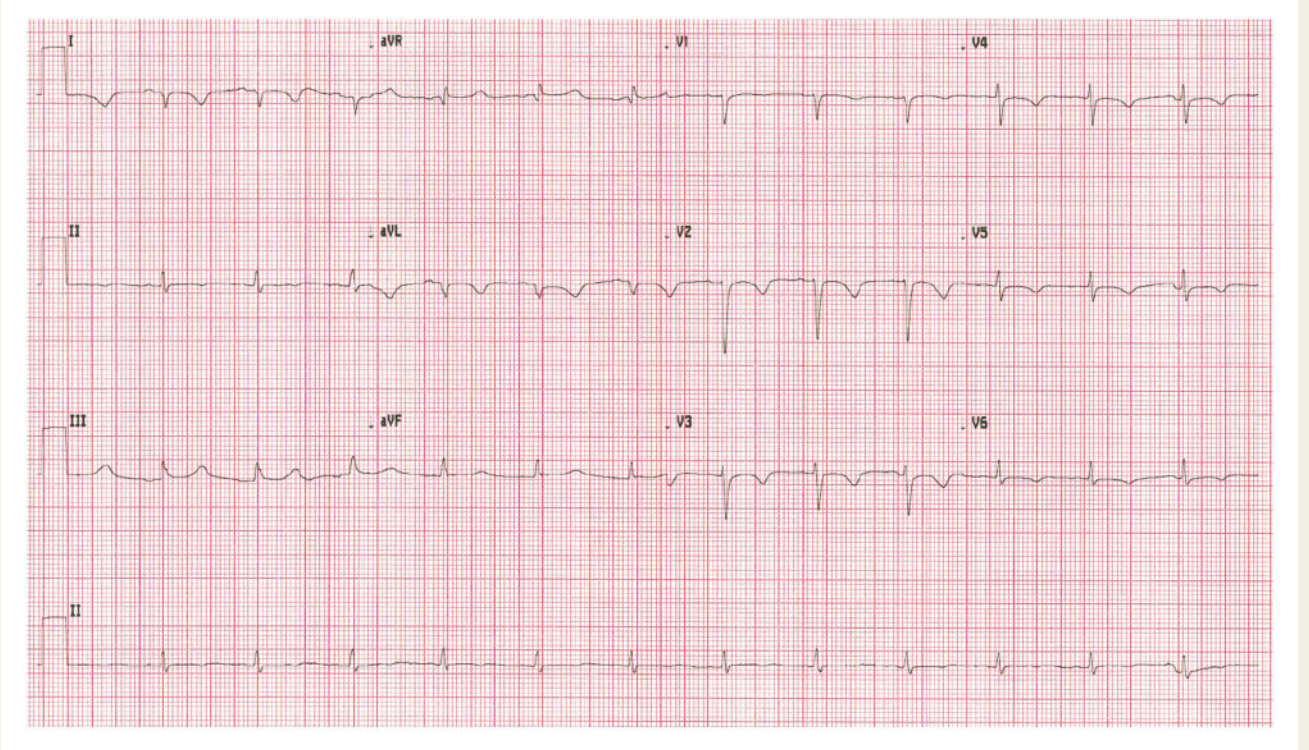


Figure 2 Twelve-lead electrocardiogram showing sinus rhythm with right axis deviation, poor R wave progression, T-wave inversion in all precordial leads and I+AVL and QTc prolongation (470 ms).

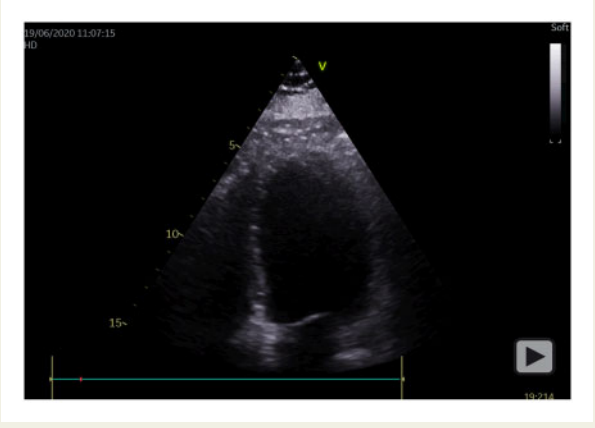
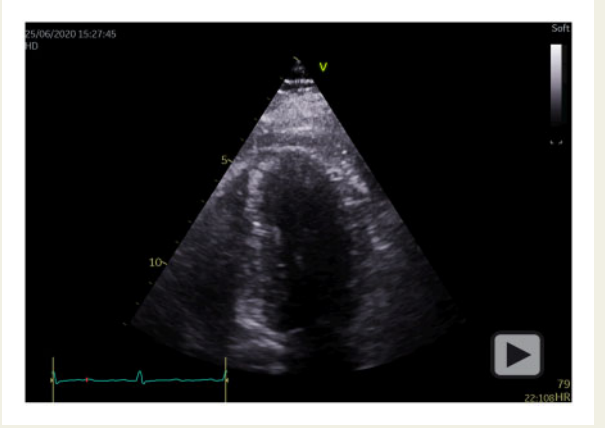


Figure 3 Echocardiogram after clinical improvement showing completely normal cardiac function with no regional wall motion abnormalities.



Video 2 Clip showing echocardiogram Day 7 - completely normal cardiac function with no RWMAs

The catecholamine surge usually seen in TS leads to a form of myocardial stunning.[8] This theory is based on the presence of a larger beta-2 to beta-1 receptor ratio in the apex of the myocardium in comparison to the base. These beta-2 adrenoceptors exhibit a biphasic response when stimulated: a positive ionotropic effect in response to low concentrations of catecholamines and a negative ionotropic effect in response to higher concentrations. Therefore, a surge in the level of circulating adrenaline results in the depression of apical myocardial contractility, leading to the characteristic ballooning seen in TS.

Pyruvate carboxylase is a mitochondrial enzyme that is involved in gluconeogenesis and energy production. This enzyme catalyzes the conversion of pyruvate to oxaloacetate when abundant acetyl CoA is available (*Figure 5*),[9] and the excess pyruvate is converted to lactate. When there is a deficiency in pyruvate carboxylase, this leads to

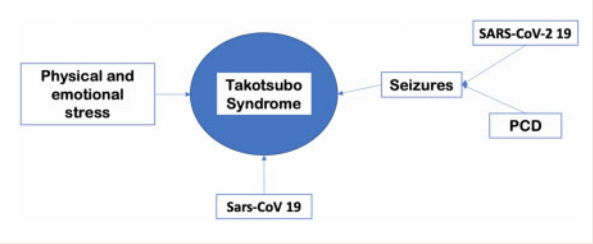


Figure 4 Diagram demonstrating the potential factors that may have led to Takotsubo syndrome in our patient

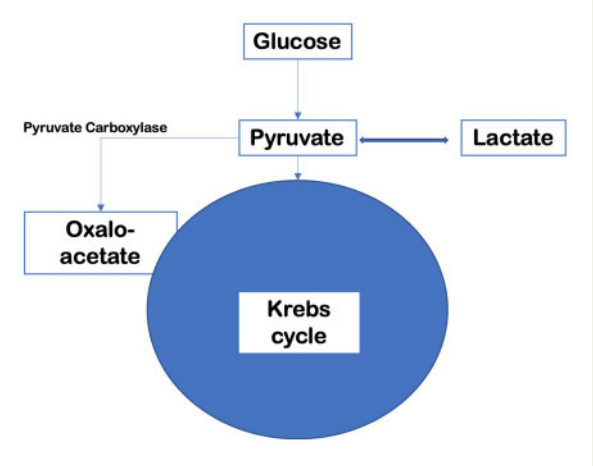


Figure 5 Simplified diagram demonstrating role of pyruvate carboxylase.

an excess of pyruvate, which is broken down to lactate within cells. This would explain our patient's high lactate on admission. Hyperlactataemia can damage tissues and organs and when the neurological system is affected, this leads to the recurrent seizures seen in patients with PCD.[10]

There have been reports of TS after seizures in the literature.[11,12] In fact, a large nationwide population-based study with 981 571 cases of epilepsy-related hospitalizations, showed that the rate of TS in these patients was 1 in 1000 and showed poor inpatient outcomes.[13] In addition, females with a neurological diagnosis appear to be at higher risk of developing TS.[14] A case series based on 39 cases of TS after seizures showed that 85% were female, 59% had a tonic-clonic or generalized seizure, and over half had an underlying neurological disorder.[15] The pathophysiology of seizure-induced TS remains uncertain. Potential theories include hormonal imbalances, microvascular spasm, or massive catecholamine release as described above.[16]

While seizures can trigger TS through the catecholamine surge, our patient who also had severe learning difficulties, which predisposes her to a greater degree of emotional stress and caused by admission to ICU. She was also unwell which subsequently leads to a physiological surge in cortisol, and hence leads to an adverse stress response.

Another contributor of TS to be considered is acute infection.[17] Although her SARS-CoV-19 swabs were negative, data have shown that the sensitivity of nasopharyngeal swabs decreases as the disease progresses.[18] The clinical suspicion remained high as she presented with a 4-day history of cough and pyrexia along with classical CT changes which suggest SARS-CoV-19 infection with no other cause being found. This underlying infection may have directly contributed to TS, or it may have increased her chance of having a seizure which subsequently led to TS. There have been two reported cases of TS in the setting of Covid-19 reported thus far and this may represent a cardiovascular manifestation of the virus.[19,20]

Conclusion

This rare presentation highlights that TS should be an important differential in patients presenting with cardiac symptoms after a seizure. With this in mind, TS should be especially considered in cardiac presentations in patients with PCD as they often suffer from recurrent seizures. In addition, TS can have multiple aetiologies and therefore a through history and examination should be carried out to identify any potential emotional or physical stresses.

Lead author biography

Dr Nikhil Sahdev is an academic foundation doctor with a keen interest in cardiology. He currently works at the Royal London Hospital and Homerton Hospital. He is a honorary research fellow at St. George's University of London.

Supplementary material

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

Acknowledgements

We would like to thank Dr Savvatis and Dr Pitcheathly for providing information for the manuscript.

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

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient's mother as the patient has severe learning difficulties in line with COPE guidance.

Conflicts of interest: none declared.

Funding: none declared.

References

1. Chazal H D, Buono MGD, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D et al. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;**72**:1955–1971.
2. Gupta S, Gupta MM. Takotsubo syndrome. *Indian Heart J* 2018;**70**:165–174.
3. Sato H. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. *Clin Asp Myocard Inj Ischemia Heart Fail* 1990;56–64.
4. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ et al. International expert consensus document on takotsubo syndrome (part i): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;**39**: 2032–2046.
5. Wang D, Yang H, De Braganca KC, Lu J, Yu Shih L, Briones P et al. The molecular basis of pyruvate carboxylase deficiency: mosaicism correlates with prolonged survival. *Mol Genet Metab* 2008;**95**:31–38.
6. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR et al. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:8–27.
7. Kato K, Lyon AR, Ghadri J-R, Templin C. Takotsubo syndrome: aetiology, presentation and treatment. *Heart* 2017; Sep 1 **103**:1461–1469.
8. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Rev Cardiol* 2008;**5**:22–29.
9. Habarou F, Brassier A, Rio M, Chrétien D, Monnot S, Barbier V et al. Pyruvate carboxylase deficiency: an underestimated cause of lactic acidosis. *Mol Genet Metab Rep* 2015;**12**:25–31.
10. Wang D, De Vivo D et al. Pyruvate carboxylase deficiency. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, K eds. Stephens *GeneReviews*®. Seattle, WA: University of Washington, Seattle; 1993. http://www.ncbi.nlm.nih.gov/books/NBK6852/ (4 July 2020).
11. Yamaguchi H, Nagase H, Yoshida S, Tokumoto S, Hayashi K, Toyoshima D et al. Acute encephalopathy with biphasic seizures and late reduced diffusion accompanied by Takotsubo cardiomyopathy. *Brain Dev* 2019;**41**:305–309.
12. Binaghi G, Congia D, Cossa S, Ganga R, Giardina G, Matta G et al. Seizures and recurrence of Takotsubo syndrome: one clinical presentation and trigger, but two different anatomical variants in the same patient. A case to meditate on. *Seizure* 2018;**63**:37–39.
13. Desai R, Singh S, Patel U, Fong HK, Kaur VP, Varma Y et al. Frequency of takotsubo cardiomyopathy in epilepsy-related hospitalizations among adults and its impact on in-hospital outcomes: a national standpoint. *Int J Cardiol* 2020;**299**: 67–70.
14. Ven FL, Pennec P-Y, Timsit S, Blanc J-J. Takotsubo syndrome associated with seizures: An underestimated cause of sudden death in epilepsy? *Int J Cardiol* 2011; **146**:475–479.
15. Stöllberger C, Wegner C, Finsterer J. Seizure-induced Takotsubo syndrome is more frequent than reported. *Int J Cardiol* 2011;**150**:359–360.
16. Blanc C, Zeller M, Cottin Y, Daubail B, Vialatte A-L, Giroud M et al. Takotsubo cardiomyopathy following acute cerebral events. *Eur Neurol* 2015;**74**:163–168.
17. Sun T-K. Infection-related stress phenomenon induced takotsubo cardiomyopathy mimicking ST elevation myocardial infarction. *J Clin Gerontol Geriatr* 2015;**6**: 106–109.
18. Jamal AJ, Mozafarihashjin M, Coomes E, Powis J, Li AX, Paterson A et al. Sensitivity of nasopharyngeal swabs and saliva for the detection of severe acute respiratory syndrome coronavirus 2. *Clin Infect Dis* 2020:doi: 10.1093/cid/ciaa848.
19. Meyer P, Degrauwe S, Van Delden C, Ghadri J-R, Templin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. *Eur Heart J* 2020;**41**: 1860.
20. Minhas AS, Scheel P, Garibaldi B, Liu G, Horton M, Jennings M et al. Takotsubo syndrome in the setting of COVID-19. *JACC Case Rep*. 2020;**2**: 1321–1325.