Takotsubo Syndrome in an Infant with Severe Hyponatremia

Takotsubo syndrome is an acute reversible cardiomyopathy characterized by left ventricular akinesia and apical ballooning or abnormalities in basal or mid-ventricular regional motion. Symptoms and ECG alterations resemble acute myocardial infarction. It is usually induced by physical or emotional stress leading to an increase in catecholamines, and it mainly affects postmenopausal women. We report the case of a 13-month male patient with Takotsubo syndrome induced by severe hyponatremia.

The patient who had a history of bilateral pyelocalyceal dilatation, consulted the reference hospital for vomiting and dehydration signs. Initial lab tests revealed leukocytosis, creatinine: 9/mg/l, Na: 108 mEq/l and K: 5 mEq/l. He received two sodium corrections, with controls 4 hours (116 mEq/L) and 18 hours later (129 mEq/L). Due to clinical deterioration, the patient was transferred to our institution 24 hours later. On admission, he presented with severe hypotension, poor peripheral perfusion, oliguria, weak central pulses and respiratory distress. The electrocardiogram showed ST-segment elevation on the left lateral wall (Figure 1). Initial echocardiography showed akinesia of mid-lateral, mid-anterior, mid-anteroseptal and apical segments. Motion was preserved in the rest of the segments. Severe deterioration of the left ventricular function was detected [left ventricular ejection fraction (LVEF) 25%] (Figure 2). Left ventricular diameters were preserved. Lat. S, 5 cm/s; medial S, 4 cm/s. Global longitudinal strain (GLS) –11% (areas of apical and anterolateral akinesia). No congenital defects. Normal coronary arteries.

Given the regional apical motion abnormality and the echocardiographic characteristics, a diagnosis of Takotsubo syndrome was considered. Serology and cultures were negative. ProBNP was 49,705 pg/ml, CPK was 90 U/l, initial troponin I was 731 ng/l at and at 24 h: 1001 ng/l, with progressive decrease on the 6th day: 107 ng/l (normal <19 ng/l). Magnetic resonance imaging scan was performed on the 5th day, reporting signs suggestive of myocardial edema in the fat suppression sequences and hyperemia in the pre- and post-gadolinium T1 sequences. Delayed enhancement was negative. The LVEF was 68%. No regional motion abnormalities were observed.

After 48 hours, normalization of the ST-segment, flat T-wave, long QTc (Figure 5) and improvement of global ventricular function were evidenced, with persistence of abnormal GLS in apical and midventricular segments. Global longitudinal strain and ventricular function were normal on the 8th day (Figure 3).

The patient presented with neurological involvement since admission, with altered sensorium. Meningitis was ruled out. The patient presented with seizures and signs of decortication after 72 hours, with a disorganized EEG and slowed rhythmicity. Due to severe neurological involvement and a history of severe hyponatremia, the MRI of the brain confirmed pontine myelinolysis. Nephrologists and urologists considered that the severe hyponatremia was possibly due to the obstructive urological disease. The patient remained hospitalized under multidisciplinary management.

Takotsubo syndrome, also called ‘stress cardiomyopathy’ or ‘apical ballooning syndrome’, is a cardiomyopathy characterized by severe ventricular dys-
function that improves over several days or weeks, induced by physical or emotional stress. A prevalence of 1.7% - 2% of patients with acute coronary syndrome -mainly women >55 years old- is estimated. Its prevalence in children has not been established. (1)

From the clinical viewpoint, this condition resembles an acute coronary syndrome, but in children it is similar to acute myocarditis. Modified Mayo Clinic diagnostic criteria include: hypokinesia, akinesia or dyskinesia presenting as left apical ballooning or mid-ventricular and basal motion abnormalities, extending beyond a coronary territory; there is a physical or emotional trigger; neurological disorders (subarachnoid hemorrhage, ischemia or seizures) may induce it; it presents further ECG abnormalities, moderately high levels of biomarkers (troponin, CPK, pro-BNP) and no evidence of infective myocarditis. (1)

The most common ECG patterns are ST-segment elevation, diffuse T-wave inversion in the anterior and lateral wall, and prolonged QT interval. (1, 2) These abnormalities are temporary. In this case, the patient presented with marked ST-segment elevation and increased troponin levels, which decreased in subsequent days and were almost normal at the first week.

Patients with Takotsubo syndrome have abnormally high serum levels of plasma catecholamines generated by previous physical or emotional stress. It has been shown that the density of left ventricular beta-adrenergic receptors is higher in the apex, suggesting that it is more sensitive to high levels of catecholamines. This can not only reduce coronary flow, (1) but also produce a negative inotropic effect at high doses of catecholamines (it triggers a switch of intracellular signaling from β2-adrenoceptor Gs protein coupling to Gi protein), which seems to protect against apoptotic effects. (3) This explains the selective involvement of cardiac function and its temporary character. Other mechanisms such as microvascular dysfunction and coronary spasm have also been described. (1)

In a review of 37 reported cases of Takotsubo in children, underlying neurological disorder was evidenced as the most common trigger of the event (surgery, acute hemorrhages, trauma or hypoxia). Other triggering factors included sepsis, urolithiasis, peri-cardiocentesis, emotional stress, and drugs such as atomoxetine and anesthetics. (4)

Only a few cases were associated with hyponatremia. Severe hyponatremia may cause altered sensorium, seizures, and other neurological manifestations. Cardiac manifestations are rare; however, cases of Takotsubo with sodium levels of 105 mEq/L have been reported. (5) In our patient, baseline serum Na+ level was 108mEq/L.

The mechanism of how hyponatremia leads to excessive catecholamines remains unclear. It has been suggested that central nervous system dysfunction secondary to hyponatremia can result in myocardial injury due to elevated catecholamine release. Another mechanism would be associated to intracellular calcium overload due to altered Na+/Ca2+ pump in the myocyte membrane. (5) In our patient, the severe neurological damage secondary to severe hyponatremia could have triggered high levels of catecholamines and induced the cardiomyopathy.

Echocardiographic findings of severe dysfunction with apical akinesia were typical. Initial longitudinal strain showed the alteration of not only apical but also midventricular segments. Echocardiographic controls in subsequent days showed improvement in systolic function at 48 h, although alteration of the deformity persisted. The recovery of function was reached within 8 days, with normal GLS in the regions previously affected.

Studies evaluating GLS in the acute phase of Takotsubo in adult patients associated a basal-lateral strain > −10 and mid-lateral strain > −7 with major adverse cardiovascular events. (6) It was evident that although LVEF seemed completely resolved, the analysis of the myocardial deformation showed delayed recovery. This may help determine the duration of follow-up for these patients.

Severe hyponatremia can present not only neurological manifestations, but also potentially produce an effect on the myocardium secondary to increased catecholamine secretion. Takotsubo syndrome is rare in children; however, it should be considered in cases of severe hyponatremia and ECG abnormalities. It is diagnosed with the typical regional apical motion abnormality detected by 2D echocardiography. Assessment of longitudinal strain can detect subtle abnormalities and determine the duration of follow-up.

**Conflicts of interest**

None declared.

(See authors’ conflicts of interest forms on the website/Supplementary material).

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Bilateral Partial Anomalous Venous Drainage in an Adult Patient: a Rare Entity

Partial anomalous pulmonary venous connection (PAPVC) is a rare, often underdiagnosed entity, in which one or more pulmonary veins are connected to the systemic venous return.

We report the case of a 27-year-old female patient with no cardiovascular risk factors and a history of asthma in her childhood.

The patient was clinically symptomatic for progressive dyspnea FCII-III; physical examination revealed wide splitting of R2, ejection systolic murmur +++++/++++ at the base, with symmetrical peripheral pulses. Additional tests included an electrocardiogram (ECG) showing signs of right ventricular (RV) overload, and a chest X-ray showing moderate cardiomegaly and enlarged right atrium. Doppler echocardiography revealed enlarged right chambers and extremely enlarged right ventricle with no evidence of intracardiac shunts, indirect signs of moderate systolic pulmonary artery hypertension, and good biventricular function. The suprasternal axis view showed an image consistent with ascending venous flow draining into the innominate vein.

In order to rule out causes for RV overload, an angiogram was performed that revealed anomalous connection of the right superior pulmonary vein to the superior vena cava, and of the left superior pulmonary vein to the innominate vein (Figure 1A and B). The upper and mid-right lobe drained into the right superior vein, and the upper lobe and lingula drained into the left superior pulmonary vein. The findings were also confirmed by digital angiography (Figure 1C and D).

With a diagnosis of bilateral partial pulmonary venous return anomaly, corrective surgery was performed. The anomalies described above were evident during surgery (Figure 2A and B). This was performed under extracorporeal circulation, which consisted of right superior pulmonary vein tunneling with autologous pericardial patch, creating an atrial septal defect (ASD) to the left atrium (LA) (Figure 2C); the drainage in the innominate vein was also closed on the left side, and anastomosis of the left superior pulmonary vein to the left atrial appendage was performed (Figure 2D).

After an uneventful postoperative course, the patient was discharged on the 5th day, with favorable outcome and early return to normal activities. Follow-up computed tomography scan showed good pulmonary drainage reconstruction.

Partial anomalous pulmonary venous connection
is a congenital defect observed in 0.4% - 0.7% of autopsies. (1, 2, 4, 6) This rare condition is characterized by one or more pulmonary veins connected to the right chambers, generally involving right pulmonary veins. Anomalous drainage of the left pulmonary veins has been reported in only 10% - 18% of the cases. (2, 6) Bilateral anomalous connection is a rare anatomical finding that represents 0.9% - 1.6% of the cases reported. (2, 3)

Symptoms and severity of the PAPVC clinical condition relate to the magnitude of left-to-right shunting; (5) dyspnea, exercise intolerance, trepidation, and progressive pulmonary hypertension are its common manifestations. (4, 5, 6) It is often associated with other congenital anomalies such as ASD. The venous sinus type ASD is found in 49% to 85% of cases and the ostium secundum type ASD in 10% to 33%. (5)

In the presence of RV overload and in the absence of intracardiac shunt, PAPVC is one of the diagnoses to be ruled out. Sensitivity of transthoracic Doppler echocardiography is low, and its usefulness to evaluate pulmonary venous return is limited among the adult population. (6) Transesophageal echocardiography, on the other hand, allows a correct assessment of the pulmonary venous return, although it has relative usefulness in case of anomalous drainage in left vertical veins. Magnetic resonance angiography and cardiac magnetic resonance imaging are the non-invasive methods of choice in the evaluation of pulmonary venous return (Class I). (6)

The indication for surgery in PAPVC is controversial. The authors agree that, if there is anomalous drainage in more than one vein, there will be significant hemodynamic consequences; therefore, surgical repair is recommended in those cases. (5, 6) Each pulmonary vein provides between 20% to 25% of the venous flow; so more than one vein with anomalous connection would mean more than 50% involvement. Conversely, if less than 50% of the flow is involved, patients tend to be oligosymptomatic until adulthood, when they will become symptomatic coinciding with increased stiffness of the left ventricle and increased left atrial pressure.

Conversely, yearly screening is indicated in asymptomatic patients with no significant hemodynamic involvement.

We can confirm that surgery is indicated in symptomatic patients or in those with >50% of anomalous venous flow involved, in the presence of a QP/QS >1.5/1, in the case of pulmonary arterial hypertension <50% of the systemic hypertension, and pulmonary resistances lower than 1/3 of systemic resistances.

The correct diagnosis and assessment of the connection sites have important implications for surgical decision.

Different surgical techniques have been described so far, including the division of the superior vena cava, tunneling of the pulmonary veins towards the LA using a pericardial patch (1-patch or double-patch technique). Warden’s surgery, consisting of the division of the superior vena cava (SVC) and its anastomosis in the RA, (4, 6) and modifications of these techniques.

In the case of our patient, two combined techniques were performed for anatomical resolution of the anomaly, with positive outcomes.

In the follow-up of surgical patients, decreased volume and IV remodeling was observed from the time of surgery to an average of 2.5 years later, (6) as well as improved functional class, and a drop of 1-2 mmHg in systolic pulmonary arterial pressure.

Postoperative complications include SVC obstruction (5%), pulmonary veins closely associated to the size of the buffle employed and the use of a double patch (12%). The incidence of tachyarrhythmia or sinus node disease has also been associated with the technique used and to the presence of previous arrhythmia, reaching between 12% and 25% depending on the series. (4)

In the immediate postoperative period, our patient had no complications, with improvement of RV volumes and reduction of systolic pulmonary artery pressure.

In conclusion, the case of this patient with bilateral partial anomalous drainage is a considerably particular entity, especially in adult patients. We believe that intensive assessment and therapy pre-planning is a cornerstone for the resolution of highly uncommon cases, in order to reduce morbidity and optimize long-term outcomes.

Conflicts of interest
None declared.

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Simultaneous Multi-Vessel Coronary Thrombosis Resolved with Rescue Angioplasty

Simultaneous multi-vessel coronary thrombosis is a poorly described entity of ST-segment elevation myocardial infarction (STEMI); consequently, clinical presentation, therapeutic approach and prognosis are not clearly known. Published case reports often describe critically ill patients with electrical and/or hemodynamic instability, most of whom were appropriately revascularized through percutaneous coronary angioplasty showing a low in-hospital mortality. We report the case of a patient with simultaneous thrombosis of the left anterior descending coronary artery and right coronary artery that was opportunistically treated at our hospital.

Simultaneous multi-vessel coronary thrombosis is defined as STEMI associated with direct angiographic visualization of two or more thrombi causing partial or complete occlusion of at least two major epicardial coronary arteries. (1) Little is known about its clinical presentation and therapeutic management. Two systematic reviews published in 2009 and 2015 included a population of 47 and 56 patients with unidentifiable etiology of simultaneous multi-vessel coronary thrombosis, which means the population whose myocardial infarction was caused by coronary atherosclerotic plaque rupture but not by other secondary causes. Electrical and hemodynamic instability was the most common clinical presentation, however, there was low percentage of in-hospital mortality. (1, 2)

We describe the case of a 68-year-old man with a history of smoking and type 2 diabetes mellitus, without any other personal or family history of diseases, who presented at the emergency department with one hour episode of chest pain, dyspnea and diaphoresis. On examination, the heart rate was 40 beats per minute (bpm) with mean arterial pressure of 70 mmHg. He was anxious and showed bradycardia with normal breath sounds on auscultation; the rest of the examination was normal. Initial electrocardiogram (ECG) revealed subepicardial lesion of the anterior and inferior wall with right ventricular (RV) involvement, as shown (Figure 1). Treatment with aspirin 300 mg, clopidogrel 300 mg, enoxaparin 30 mg and a weight adjusted single bolus of tenecteplase within the first 15 minutes of the diagnosis of myocardial infarction was administrated. However, the patient developed cardiogenic shock and the electrocardiogram did not show any reperfusion criteria after 60 minutes of thrombolysis. At that moment, STEMI risk scores were GRACE 181 points (40% probability of death from admission to 6 months) and TIMI 9 points (35.9% risk of all-cause mortality at 30 days). Therefore, the patient was transferred to the cardiac catheterization laboratory to undergo a rescue angioplasty supported by norepinephrine and dobutamine. First, a pacemaker electrode was placed in the right ventricle through the femoral vein and was programmed in VVI mode at 70 bpm; coronary angiography showed intraluminal thrombus and 70% stenosis in the proximal segment of the right coronary artery (RCA) with TIMI 2 flow. Simultaneously, the left anterior descending artery (LAD) showed intraluminal thrombus and 80% stenosis in the mid-segment with TIMI 2 flow. Everolimus-eluting stent (Xience-Alpine: 4.0 x 28 mm) was implanted in the RCA and two everolimus-eluting stents (Xience-Alpine: 3.5 x 18 mm and 4.0 x 18 mm) were implanted in the LAD with stent overlap. The final angiography showed both arteries with TIMI 3 flow (Figure 2). Subsequently, the ECG showed normal sinus rhythm and markers of reperfusion with normalization of ST-segment and T wave inversions in the affected leads. The echocardiogram revealed RV dyskinesia with fractional area change of 22% and left ventricular ejection fraction of 46%. The inotropic support and the vasopressor were withdrawn in less than 48 hours. Finally, after cardiac in-hospital rehabilitation, he was discharged 8 days later with medical follow-up in the outpatient cardiology clinic. In the last cardiology consultation, six months after the event, the patient denies cardiovascular symptoms in his daily activities or during the aerobic exercises, so his condition has a functional class I, according to the New York Heart Association.

Obstructive coronary artery disease in other epicardial arteries unrelated to STEMI is a common finding and has been found approximately in 52.8% of cases. (3) However, simultaneous multi-vessel coronary thrombosis is a rare entity of STEMI, which has been reported in 1.7% to 4.8% of cases. (2) The specific trigger of this condition remains unclear, but a theory suggests that inflammatory pathophysiological processes exert adverse effects throughout the coronary

![Fig. 1. Initial ECG: A) ST-segment elevation in leads DII, DIII, AVF, V1-V6, DI + AV dissociation. B) V3R and V4R with ST-segment elevation + Qr + ST.](image-url)
vascularity and therefore result in multiple unstable lesions with multi-vessel thrombosis. (4) In two systematic reviews, the most frequent clinical presentation was cardiogenic shock (36% to 41%), followed by ventricular arrhythmias (23% to 25%). The ECG generally reveals ST-segment elevation in leads of a single wall affected, and less frequently in leads of all the walls involved. On the other hand, the therapeutic approach in most of these patients has consisted of percutaneous coronary intervention in up to 91% of the cases. Despite the severity of the clinical presentation, in-hospital mortality has varied from 1% to 5% of cases. (1, 2) There is a discrepancy between the severity of the clinical presentation and inpatient mortality, as the presence of cardiogenic shock during STEMI carries a risk of in-hospital mortality greater than 60%. (5) This may be due to the fact that many cases of patients dying from simultaneous multi-vessel coronary thrombosis have not been published, (1) or many of them develop with sudden death before a coronary angiography procedure. (2)

In conclusion, this particular case had a favorable evolution despite the severity of the clinical presentation with similar outcome to other case reports of simultaneous multi-vessel coronary thrombosis who were opportunistically revascularized.

Conflicts of interest
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Fig. 2. Transient pacemaker in the right ventricle + Coronary angioplasty: A) Right coronary artery: 70% stenosis in the proximal segment + thrombus images. B) Left anterior descending coronary artery: 80% stenosis in the mid-segment + thrombus images. C, D) Everolimus-eluting stents (Xience-Alpine) were implanted in both coronary arteries.

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