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Case Study

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TAKOTSUBO SYNDROME IS A COMPLICATION OF ACUTE ALCOHOL WITHDRAWAL

Amin Ahminedache[1]*, M.D, Saeed Hatem, M.D[1], Honoré Kabuya Buana[2] and Mohammed Cherti[1], M.D.

[1]Cardiology B Department, Maternité Souissi, Ibn Sina University Hospital Boulevard Ibn Rochd, Agdal-Hay Ryad 10.000 Rabat, Morocco.

[2]Medical Intensive Care unit, Ibn Sina University Hospital, Rue Lamfedal Cherkaoui, 10.000 Rabat, Morocco.

***Corresponding Author: Amin Ahminedache**

Cardiology B Department, Maternité Souissi, Ibn Sina University Hospital Boulevard Ibn Rochd, Agdal-Hay Ryad 10.000 Rabat, Morocco.

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ABSTRACT

Acute alcohol withdrawal (AAW) breaks the neuroadaptive mechanisms to chronic alcoholism resulting in a hyper adrenergic environment, which is a breeding ground for the occurrence of Takotsubo (TTS) syndrome and life threatening ventricular arrhythmias. We report a case of a 49-year-old woman who presented TTS following AAW complicated by acute heart failure and ventricular arrhythmias with a brief review of the literature on the subject.

KEYWORDS: Acute alcohol withdrawal, Stress cardiomyopathy, takotsubo syndrome, cathecolamines.

INTRODUCTION

Acute alcohol withdrawal (AAW) breaks the neuro-adaptive mechanisms that have developed during chronic alcohol consumption, resulting in a adrenergic discharge responsible for neurovegetative clinical manifestations that could be severe and life-threatening. Whereas, Takotsubo syndrome (TTS) is characterized by an acute reversible myocardial stunning related to an adrenergic discharge most often occurring during physical or emotional stress or acute medical conditions. We report a case of a 49-year-old woman who presented TTS following AAW complicated by acute heart failure and ventricular arrhythmias with a brief review of the literature on the subject.

CASE REPORT

A 49 years old female was brought to the emergency room by ambulance after presenting a first episode of tonic-clonic seizures at home witnessed by the firefighters. Her medical history was significant for anxiety and depression for which a pharmacological treatment was stopped two years earlier. 48 hours before her admission she spontaneously stopped drinking alcohol after a consumption of 4 to 5 glasses of whiskey per day for 7 years. She had smoked half a pack of cigarettes for 2 years at her teenage. On admission, she was cooperative, time and space oriented with a Glasgow coma score of 15/15, her blood pressure was of 141/99mmHg, Heart rate of 115bpm, temperature of 36.7°C, respiratory rate of 15 cpm and oxygen saturation at 96%. Neurological exam found a mild tremor but no focal signs. Heart, lungs and abdomen examination was unremarkable. In the emergency room, 4 short recurrences of 10 seconds tonic-clonic seizures were noted with a rapid and complete recovery of consciousness without neurological deficit. An Emergency CT head scan was normal. ECG showed a 102 bpm sinus tachycardia, a prolonged QTc interval of 539ms, no conduction nor repolarization abnormalities were noted *(figure 1)*. Blood tests results were as follow: Hemoglobin: 9.7g/L, MCV: 115fL; MCH: 38pg, MCHC: 32.9g/dL; WBC: $3.8x10^9$/L; PLT: $260x10^9$/L; Na: 144mmol/l; K: 2.6mmol/l; BUN: 2.8mmol/l; Glucose: 5.8mmol/l; total proteins: 50g/L; albumin: 25.4g/L; Ca: 1.93mmol/l; AST: 77U/L; ALT: 35U/L; ALP: 118U/L; LDH: 150U/L; CRP: 11mg/L, High Sensitivity troponin: 32ng/L. Clonazepam infusion and intra-venous potassium supplementation were started and the patient was transferred to the intensive care unit. On arrival to the ICU, the patient presented a sustained torsade de pointe with hemodynamical unstability that resolved after one external electric choc *(Figure 1)*. The patient was intubated and placed under mechanical ventilation in anticipation of neurological and hemodynamic deterioration. The treatment of hypokalemia was intensified and magnesium supplementation was added. On day 2, a second sustained episode of torsade de pointe with hemodynamical instability reoccurred and was electro-converted successfully to a sinus rhythm. ECG showed changes with an ST segment elevation in aVL and V2 and a T wave inversion in D1, aVL, V1 and V2 *(figure 1)*. ETT showed akinesis of left ventricular apical and mid segments and a ballooning aspect with an EF of 20% *(Figure 2)*. Urgent coronary angiography found normal epicardial vessels. Left ventriculogram was not performed. High Sensitivity troponin was of 1141ng/L and serum potassium of 3.4mmol/L. Ramipril was introduced. The same day, the patient presented

signs of pulmonary edema that were rapidly controlled with low dose IV furosemide. On day 3, the ST segment in aVL and V2 was back to normal and deep negative T waves were noted on D1, aVL and V2 with a persistent long QT. On Day 4, after extubation, an agitated behavior was managed by oral diazepam and vitamin therapy. 10 days after the admission, the patients was asymptomatic, repolarization was normal except for a flat T wave on aVL, QTc interval was of 461ms. Left ventricle had dramatically recoevred contractility and EF was 55%. The patient was discharged home on 5mg of ramipril and 2.5mg of bisoprolol.

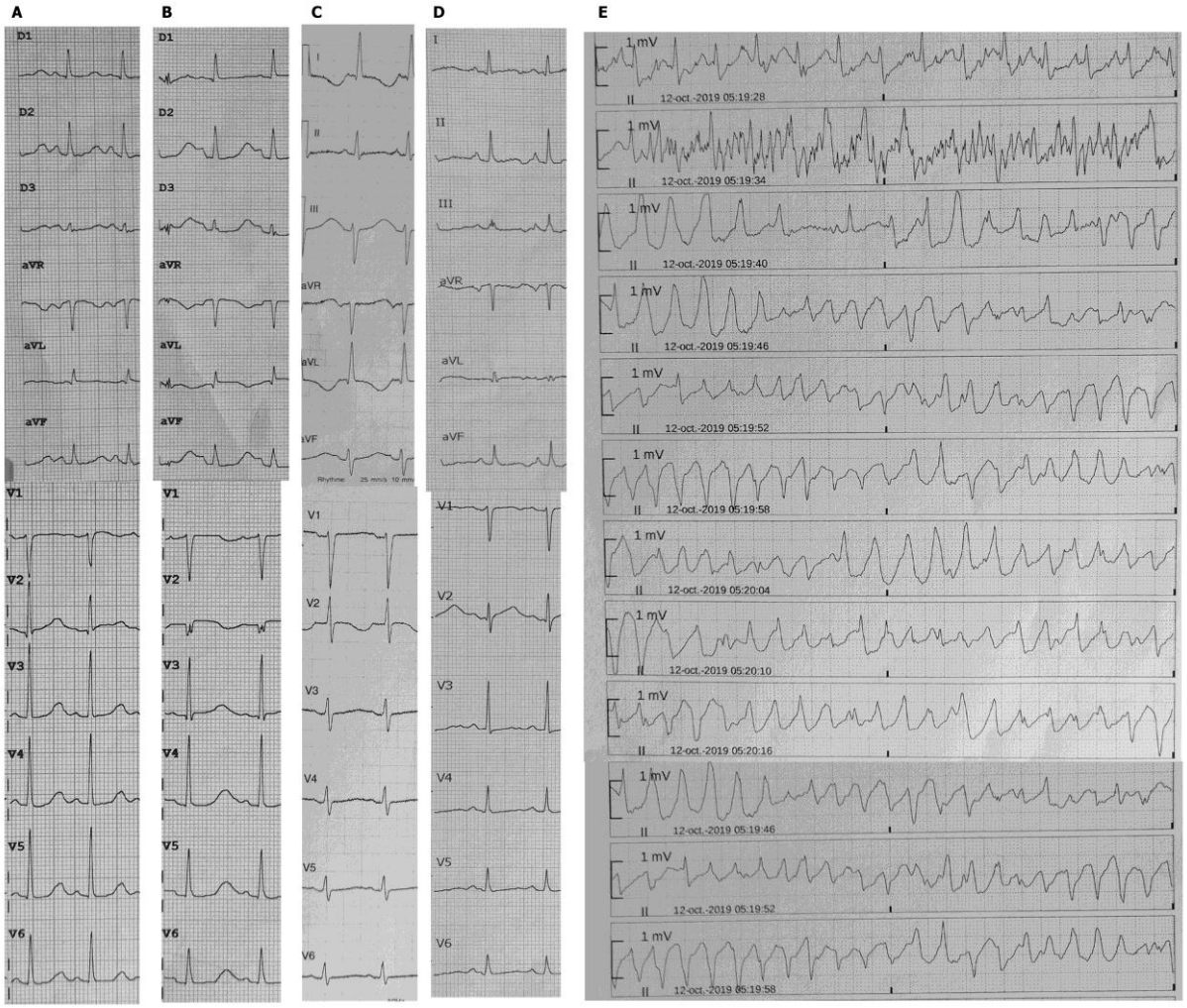

Figure 1: Electrocardiographic evolution: *A:* 12 lead ECG at the admission showing a long QT interval of 539ms and a normal repolarization. *B:* 12 lead ECG recorded at the 2nd day of admission showing repolarization abnormalities not corresponding to a single vascular territory: an ST segment elevation in V2 and aVL with a fragmented QS aspect on V2, negative T waves in V1,V2, aVL and flat T wave in D1. QTc interval of 639ms. *C*: on the 3rd day, ST segment and V2 QRS complex were back to normal and appearance of inverted T waves in V1,D1 and aVL. QTc= 610ms. *D:* 12 lead ECG at the 10th day showing no significant repolarization abnormalities and a QTc of 461ms. *E:* Telemetry recording of a torsade-de-pointes/ventricular fibrillation, which required electrical cardioversion.

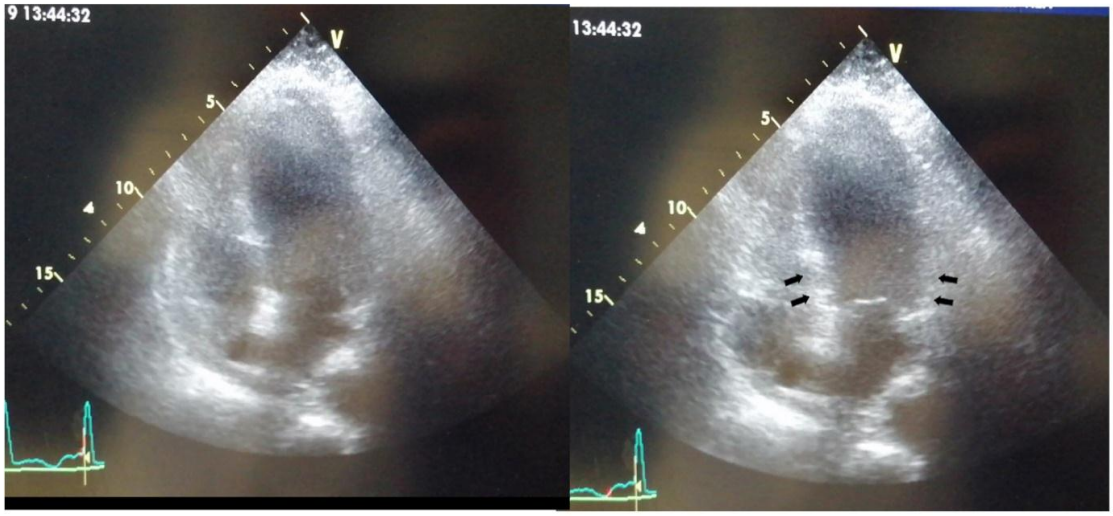

Figure 2: **Trans-thoracic echocardiography performed at the second day of admission showing an apical ballooning aspect due to the lost of apical and middle segments wall motions.**

DISCUSSION

The clinical presentation of TTS mimics an acute coronary syndrome. It is an exclusion diagnosis after ruling out coronary artery disease, pheochromocytoma and myocarditis. A recent international expert consensus defined the diagnosis criteria of the condition.[1] *(Table 1).*

Table 1: International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

1. Patients show transient 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)
2. An emotional, physical, or combined trigger can precede the takotsubo syndrome 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 takotsubo syndrome.
4. New ECG abnormalities are present (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 takotsubo syndrome.
7. Patients have no evidence of infectious myocarditis.
8. Postmenopausal women are predominantly affected.

Pathophysiological mechanisms of TTS have not been fully elucidated. An excess release of catecholamine is the most accepted Hypothesis.[2] Myocardial injury can be the result of several mechanisms: epicardial vessels spasm[3], endothelial dysfunction[4] and direct cathecolamines toxicity on cardiomyocytes.[5] The distribution of β1 and β2 receptors in the left ventricle could explain this characteristic left ventricular involvement.

Acute alcohol consumption decrease central nervous system activity by potentiating neuro-depressant GABA-ergic activity and inhibiting NMDA excitatory system of N-methyl-D-aspartate (NMDA). To restore neurochemical balance when the consumption is prolonged in the long term, compensatory mechanism occur decrease the sensitivity of GABA receptors and increases the number of NMDA receptors. Acute alcohol withdrawal (AAW) disrupts this balance and creates a state of neuronal hyper excitability with increased levels of catecholamines and adrenergic receptors sensitivity unopposed by the inhibited inhibitory mechanism responsible for the clinical symptoms that occur between 8 to 48 after the AAW (Tachycardia, hypertension, tremor, agitation, hallucinations, and seizures).[6,7]

The intersection of AAW and TTS pathophysiology at the surge of cathecolamines is consistent with occurrence of TTS in the present case. It also suggests that the rare cases reported in medical literature do not reflect the true incidence of TTS in AAW. This could be explained by the lack of awareness of TTS among medical

professionals that manage AAW patients, and the absence of routine cardiac monitoring.

Joy has shown that the development of a delirium tremens (DT), which is the most severe form of AAW, is a risk factor for acute onset of TTS compared to the AAW patients who didn't develop a DT.[8] Besides, our case presented repeated tonic-clonic seizures that present a trigger of TTS independently of AAW.[9]

Recent data shows that mortality rate in TTS are similar to acute coronary syndromes.[10] In DT, mortality rate has been decreased to 5% with the advent of pharmacological sedation.[11] Those high mortality rates are explained in part by life-threatening ventricular arrhythmias occurring in the context of high catecholamine levels. In a similar way, both AAW and TTS are associated with prolonged QT interval, torsade de pointe, Ventricular tachycardia and ventricular fibrillation. Low serum potassium level is another common finding in both conditions that increase the risk of occurrence of serious cardiac arrhythmias.[12,13] There is no data that compares the rate of occurrence of serious ventricular arrhythmias in AAW and TTS separately and when TTS is AAW induced. We could think that the risk is additive and we suggest that all AAW should receive a cardiac monitoring specially those presenting a prolonged QT interval and hypokalemia. In the present case, the first sign of cardiac involvement was the occurrence of a sustained hemodynamically untolerated torsade de pointe – ventricular fibrillation that required an external electric choc. Potassium level remained low despite a potassium- magnesium supplementation which resulted in the occurrence of a second episode of torsade de pointe.

In this setting of adrenergic hyperactivity, sympathetic blockade seem to be a reasonable therapeutic choice. In AAW, the use of atenolol in combination with oxazepam has enabled a faster normalization of alteration in vital signs and a reduction in neurovegetative disturbances.[14] Propanolol showed to be as effective as diazepam on physical symptoms of AAW.[15] No data is available on the effectiveness of beta blockers in preventing cardiac arrhythmias or TTS during AAW. Animal models of TTS have shown that the administration of alpha and beta blockers improve the apical ballooning.[16] However, in patients with long QT interval, the use of beta-blockers must be cautious as it could trigger arrhythmias. In the present case, Beta blockers were not introduced till the QT interval fell under 500ms. No data is available neither on the effectiveness of beta blockers in preventing cardiac arrhythmias or TTS during AAW nor on their overall benefit on mortality on both conditions.

CONCLUSION

The Hyper adrenergic environment associated with AAW may be considered a risk factor for TTS especially in patients presenting a delirium tremens and/or seizures. Ventricular life threatening arrhythmias are common and are promoted by hypokalemia. We recommend clinical, electric and biological cardiac monitoring in all AAW patients. Aggressive correction of hypokalemia is essential in preventing arrhythmias. Beta blockers were associated with clinical improvement in AAW and TTS separately; but their use should be cautious in patients with long QT.

CONFLICT OF INTEREST AND SOURCE OF FUNDING

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REFERENCES

1. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus document on Tqkotsubo syndrome (part I): Clinical characteristics, Diagnostic criteria and pathophysiology. European Heart Journal, 2018; 39: 2032–2046.
2. H. M. Nef, H. M¨ollmann, Y. J. Akashi, and C. W. Hamm, "Mechanisms of stress (Takotsubo) cardiomyopathy," *Nature Reviews Cardiology*, 2010; 7(4): 187–193.
3. Fiol M, Carrillo A, Rodriguez A, Herrero J, Garcia-Niebla J. Left ventricular ballooning syndrome due to vasospasm of the middle portion of the left anterior descending coronary artery. Cardiol J., 2012; 19: 314–316.
4. Kume T, Akasaka T, Kawamoto T, Yoshitani H, Watanabe N, Neishi Y, Wada N, Yoshida K. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. Circ J., 2005; 69: 934–939.
5. Shao Y, Redfors B, Stahlman M, Tang MS, Miljanovic A, Mollmann H, Troidl C, Szardien S, Hamm C, Nef H, Boren J, Omerovic E. A mouse model reveals an important role for catecholamine-induced lipotoxicity in the pathogenesis of stress induced cardiomyopathy/ Eur J Heart Fail, 2013; 15: 9–22.
6. Jesse S, Bråthen G, Ferrara M, Keindl M, Ben-Menachem E, Tanasescu R, Brodtkorb E, Hillbom M, Leone MA, Ludolph AC. Alcohol withdrawal syndrome: mechanisms, manifestations, and management. Acta Neurol Scand, 2017 Jan; 135(1): 4-16.
7. Banerjee S, Sharma K, Khanna M. Alterations in b-adrenergic receptorbinding during ethanol withdrawal. Nature, 1978; 276: 407–9.

8. Parijat S. Joy, Gagan Kumar. Delirium tremens is a risk factor for Takotsubo cardiomyopathy. Int J Cardiol, 2015 Jul 15; 191: 185-6.
9. Stollberger C, Wegner C, Finsterer J. Seizure-associated Takotsubo cardiomyopathy. Epilepsia, 2011; 52: e160–e167.
10. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tscho¨pe C, Schultheiss H-P, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Bo¨hm M, Erbel R, Cuneo A, Kuck K-H, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KEJ, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lu¨scher TF. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med, 2015; 373: 929–938.
11. L. Ng, J. Wang, L. Altaweel, and M. K. Athar, "Neurologic aspects of cardiac emergencies," *Critical Care Clinics*, 2014; 30(3): 557–584.
12. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, Bouchard JL, Kalsmith B, Garlitski AC, Tighe DA, Estes NA 3rd, Aurigemma GP, Link MS. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsades de pointes. Heart Rhythm, 2011; 8: 555–561.
13. Bär KJ, Boettger MK, Koschke M, Boettger S, Grotelüschen M, Voss A, Yeragani VK. Increased QT interval variability index in acute alcohol withdrawal. Drug Alcohol depend, 2007 Jul 10; 89(2-3): 259-66.
14. Spies CD, Dubisz N, Neumann T, et al. Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma : Results of a prospective, randomized trial. Crit Care Med., 1996; 24: 414-22.
15. Bailly D, Servant D, Blandin N, Beuscart R, Parquet PJ. Effects of beta-blocking drugs in alcohol withdrawal: a double-blind comparative study with propranolol and diazep am. Biomed Pharmacother, 1992; 46(9): 419-24.
16. Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: a possible animal model of 'Tako-Tsubo' cardiomyopathy. Circ J., 2002; 66: 712–713.