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Acute Brugada ECG Pattern Induced by Mild Amitriptyline Overdose

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Introduction

Brugada syndrome is characterized by presence of Brugada ECG pattern (BEP) and symptoms related to ventricular arrhythmia, which includes palpitations, syncope, and sudden cardiac death (SCD) [1,2]. BEP is described as right bundle branch block (RBBB) pattern and ST elevation of >2 mm in either a coved (type 1) or saddleback (type 2) morphology in the right precordial leads, specifically V1 and V2 [1-4]. Classically, this syndrome is defined by genetic mutation of SCN5A, which codes for the sodium channel (INa) in cardiac myocytes and is found in 20-30% of patients with this syndrome [1,2,5]. However, drug-induced BEP and Brugada syndrome are important causes of ventricular arrhythmia and SCD. We present a case of apparent amitriptyline-induced BEP.

Case Presentation

A 26-year-old female with a history of depression, prior suicide attempt, and uncontrolled type 1 diabetes mellitus complicated by severe polyneuropathy was found somnolent and vomiting by a family member. She reportedly consumed two to three times her prescribed dose of amitriptyline (a total of 300 - 450mg) due to acute on chronic pain syndrome. Her 12-lead ECG upon arrival to our facility (day 1) showed sinus tachycardia, right axis deviation, intraventricular conduction delay, QTc prolongation (494 msec), and 2 mm saddleback ST elevation in lead V2 (Figure 1). Unfortunately, we did not have access to a baseline ECG. She was admitted to the medical ICU, treated with intravenous fluids and sodium bicarbonate and her QTc stabilized on serial ECGs. She was discharged on day 3 and amitriptyline was replaced with duloxetine given high risk for recurrent tricyclic antidepressant overdose. On day 9, she was again found somnolent in her home and taken to an outside emergency department, where she complained of upper back pain that radiated to her chest between her breasts. Blood pressure was 132/54 mmHg and heart rate 107 bpm. Pertinent laboratory evaluation was as follows: potassium 4.7 (N: 3.5-5.0) mEq/L, magnesium 1.5 (N: 1.5-2.9) mg/dL, calcium 13.3 (N: 8.5-10.5) mg/dL, D-dimer and Troponin I were within the reference range. She was transferred to our center for further care.

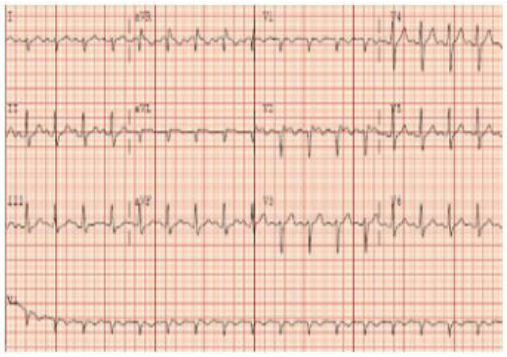

Figure 1: 12-lead ECG showing sinus tachycardia, right axis deviation, intraventricular conduction delay, QTc prolongation (494 msec), and 2 mm saddleback ST elevation in V2.

Upon arrival, she remained somnolent, vitals were relatively unchanged, and she denied taking extra doses of any medications. Pertinent laboratory evaluation included: potassium 5.3 mEq/L, magnesium 1.4 mg/dL, creatinine 1.3 (N: 0.6-1.2) mg/dL, anion gap 21, and beta-hydroxybutyrate 4.3 (N: 0.0-0.3) mEq/L, and negative urine toxicology screen. Her 12-lead ECG upon arrival showed sinus tachycardia, right axis deviation, atypical RBBB, QTc prolongation (503 msec), and 2 mm coved ST elevation in V2 (Figure 2). Echocardiography revealed normal bi-ventricular systolic function with no evidence of structural heart disease. She was admitted to the medical ICU, treated with intravenous fluids, insulin infusion, and intravenous sodium bicarbonate with serial ECGs every 4 hours for 48 hours. The electrophysiology service was consulted, and during their interview, the patient was more awake and did admit to taking 6 to 12 tablets of amitriptyline (a

total estimated dose of 300 – 600 mg) prior to the event. ECG on day 15 showed resolution of BEP, QRS duration of 100 msec, and QTc of 457 msec (Figure 3).

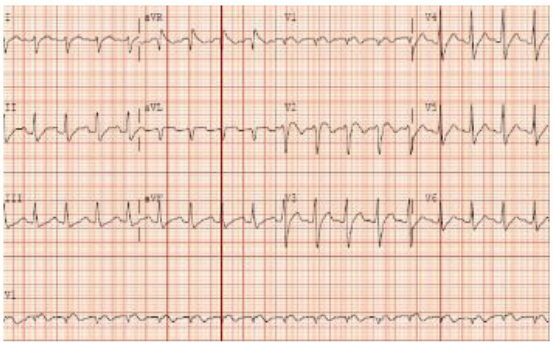

Figure 2: 12-lead ECG showing sinus tachycardia, right axis deviation, atypical RBBB, QTc prolongation (503 msec), and 2 mm coved ST elevation in V2.

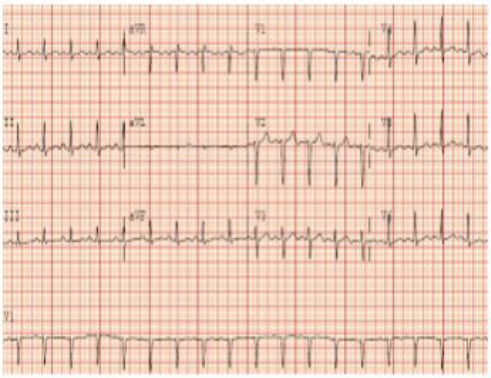

Figure 3: 12-lead ECG showing resolution of Brugada ECG pattern, with sinus tachycardia, QTc 457msec, and QRS duration 100msec.

This patient's presentation was most consistent with acute BEP secondary to amitriptyline overdose. However, it was recommended that she also undergo genetic testing for Brugada Syndrome, and consider flecainide challenge testing in the future. She was eventually transferred to Medicine-Psychiatry for further management of depression. After discharge, she was lost to follow up for the past 1 year, and did not receive any further cardiac testing to our best knowledge.

Discussion

Brugada syndrome was recognized as a clinical entity in 1992, and like long QT syndrome (LQTS), has both genetic and drug-induced mechanisms that can lead to ventricular arrhythmia [2,4]. Its prevalence is 5-10 in 10,000 and it is the underlying cause of about 20% of SCD in patients with no structural heart abnormalities [1]. Brugada ECG pattern is required for the diagnosis, and consists of RBBB pattern with ST elevation >2 mm and either high takeoff of a convex ST segment descending into an inverted T wave (type 1, coved) or an r' and upright T wave (type 2, or saddleback) [1].

As described above, genetic mutation of SCN5A, the gene that codes for cardiac myocyte inward sodium channels, causes electrophysiological pathology that results in Brugada syndrome and ventricular arrhythmias. However, case reports of drug-induced BEP or Brugada syndrome are becoming more frequent. TCAs are used for treatment of depression because of their effect of serotonin and norepinephrine reuptake inhibition, though these drugs are well known to have a significant side-effect profile relating to their effect on various H1, H2, muscarinic acetylcholine receptors, and sodium channels (INa).

There is a degree of uncertainty surrounding the true pathophysiologic mechanisms of Brugada syndrome. Two prevailing theories are 1) primary repolarization abnormality due to abbreviated refractory period allowing phase 2 re-entry and 2) primary depolarization abnormality due to localized conduction delay in the right ventricular outflow tract (RVOT), which can then trigger re-entrant tachyarrhythmia after a premature beat [1]. In either scenario, reduction in the INa current is the underlying defect. In the repolarization disorder theory, a heterogeneously diminished inward INa current causes a relatively stronger outward Ito current in the RVOT epicardium compared to the endocardium. This allows Ito to repolarize the membrane to a voltage at which L-type calcium channels are not activated, leading to a blunted phase 2 and heterogeneous dispersion of early repolarization that allows for re-entry [1,3]. The mechanism for the depolarization disorder theory stems from diminished INa current and blunted depolarization in the RVOT compared to RV. When the RV has early depolarization, it has a higher membrane potential than the RVOT, which has delayed depolarization. Re-entrant tachyarrhythmias can trigger in border zones between early and delayed depolarization, similar to the mechanism that occurs in transmural ischemia that results in membrane potential differences [1].

The association of TCAs with not only QT prolongation, but also BEP and Brugada syndrome is of particular importance when treating patients with accidental or intentional overdose; although patients with underlying genetic mutation of SCN5A and other channelopathies may be at increased risk of Brugada syndrome even with therapeutic doses of TCAs. In the case of this patient, the first time she was admitted for TCA overdose she had evidence of Brugada ECG pattern; however, this did not seem to be recognized in her medical ICU notes and only her QTc was monitored. It is critical to recognize BEP and Brugada syndrome given the high risk of mortality due to SCD and polymorphic ventricular tachycardia (PMVT), especially in younger patients who may otherwise have no risk factors for heart disease. One group sought to determine clinical characteristics of patients with drug-induced

Brugada syndrome that were reported to the website www.brugadadrugs.org [6]. Of the 74 cases identified, 77% were males with no prior history of heart disease. Lithium was the most common oral drug reported at 20% followed by amitriptyline at 16%. Five patients had reported syncope, and 10 patients had reported fever, 3 of which had VF; there was an overall 13.5% mortality rate [4]. Yet another case report highlights a patient treated for depression with nortriptyline who was evaluated for multiple episodes of syncope that were found to be secondary to PMVT when ambulatory monitoring recorded two episodes lasting 38 and 94 seconds, the latter of which resulted in syncope [5]. Flecainide challenge induced a type 1 BEP in this patient, suggesting that he had underlying channelopathy that predisposed him to Brugada syndrome, which is what likely led to initiation of PMVT in this patient.

Our case highlights the role of tricyclic anti-depressants (TCAs), specifically associated with lower-level amitriptyline overdose, in a young female with BEP on resting ECG. There are indeed various case reports of TCA related BEP, however, many of them report these findings with higher doses of TCA than our patient ingested [7]. Review of our patient's ECG from the first admission after ingestion of less than 450 mg of amitriptyline (Figure 1) reveals subtle indications of type 2 (saddleback) BEP in V2. With her second admission, quite obvious type 1 (coved) BEP was induced with ingestion of only 600mg of amitriptyline (Figure 2). In comparison, one retrospective study included 65 cases of intentional TCA overdose over a 35-month period, and found that 15% of patients had type 1 BEP; 66% of cases involved amitriptyline with mean dose of 749mg +/- 436mg [8]. It is unfortunate that the patient described above did not return for induction or genetic testing, as she may have some underlying genetic predisposition to development of BEP.

Conclusion

Recognition of all TCAs as potential culprits in ventricular arrhythmias secondary not only to prolonged QT, but also to channelopathies such as Brugada syndrome, is crucial for appropriate monitoring in patients who overdose on these medications at any dose. The true mortality risk in cases of Brugada syndrome induced by TCAs is not well-elucidated, but nonetheless, there is a risk of SCD not related to structural or ischemic heart disease that is potentially preventable if appropriate recognition, monitoring, and treatment take place. It is therefore important to increase awareness of other less common, though not less deadly, genetic and drug-induced causes of ventricular arrhythmia, such as Brugada syndrome.

Authors' Contributions

Dr. Adams and Dr. Bin Abdulhak were responsible for the concept of this article, drafting the manuscript, and collecting images and data. Dr. Gebska and Dr. Giudici provided critical revision of the article with expert opinions, as well as approval of the final manuscript.

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None

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