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INTERMEDIATE

CASE REPORT: CLINICAL CASE

The Brugada Type 1 Electrocardiogram and Ventricular Tachycardia With High-Dose Amitriptyline

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ABSTRACT

A 32-year-old woman with anorexia nervosa experienced ventricular tachycardia while on therapeutic-dose amitriptyline despite normal blood tests, imaging, and intracardiac recordings. Electrocardiograms over several years featured the Type 1 Brugada pattern. Careful electrocardiogram monitoring should be made if using high doses of amitriptyline, especially in those with low body weight. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:156–61)

We present the case of a 32-year-old woman with anorexia nervosa, presenting with ventricular tachycardia (VT) on the fourth day of a refeeding regimen. She had been admitted as a voluntary inpatient at an eating disorders unit, and was on a high dose of amitriptyline (250 mg once daily or 7.6 mg/kg/day) in the context of depression and anorexia nervosa (body mass index = 10.8 kg/m^2). The patient reported previous seizures (including nocturnal) and had in relation to these an intracranial bleed and rib fractures. She had been investigated with an electroencephalogram (results unknown) and had been diagnosed with epilepsy, for which she was taking carbamazepine 200 mg twice daily (12.1 mg/kg/day). In addition, she was also taking thiamine 100 mg (3.0 mg/kg/day) tablets once daily. This case report is made with the expressed written consent of the patient in question.

LEARNING OBJECTIVES

- To know the causes of Brugada phenocopies and consider them during the differential diagnosis.
- To understand that decision making prior to defibrillator implantation is complex and benefits from both specialist input and provision of thoughtful support to affected patients.

On the day of her symptoms she had been fed a large meal and had awoken with palpitations. She was transferred to the emergency department where an electrocardiogram (ECG) demonstrated a broad complex tachycardia at a rate of 134 beats/min (**Figure 1**). VT had been diagnosed. QRS complexes were positive in the inferior leads with left bundle branch block pattern in the precordial leads, suggesting a superior right-sided focus.

She reverted spontaneously to sinus rhythm within 10 min of arrival to the emergency department with coved ST-segment elevation of 4 mm in lead V_1 and V_2

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in a type 1 Brugada pattern (Figure 2). Corrected QT interval was prolonged at 482 ms.

Serum electrolytes were normal: sodium 135 mmol/l, potassium 4.6 mmol/l, magnesium 0.73 mmol/l, and calcium 2.34 mmol/l. A recent thyroid-stimulating hormone test was also normal: 0.85 mIU/l.

She was admitted to the hospital for monitoring and amitriptyline was discontinued and 2g of magnesium was administered intravenously. She had a further episode of VT without hemodynamic compromise, spontaneously terminating after 5 min (Figure 3).

Intervening ECGs showed sinus rhythm with further spontaneous type 1 Brugada pattern and corrected QT interval of 470 ms, measured in lead II using Bazett's formula (Figure 4).

MEDICAL HISTORY

The ECG was reviewed from an admission with "seizure" in 2016 and was clearly seen to also demonstrate a type 1 Brugada pattern (Figure 5). The patient was on the same dose of amitriptyline at this time.

Further consultation revealed a paternal uncle with hypertrophic cardiomyopathy but no family history of sudden cardiac death, epilepsy, or equivalent events.

DIFFERENTIAL DIAGNOSIS

Brugada syndrome (BrS) was considered alongside BrS phenocopy due to her competing medical conditions. An amitriptyline dose of 250 mg once daily was deemed to be especially high in the context of her low body weight, although initial serum levels were not taken.

INVESTIGATIONS

Cardiac magnetic resonance imaging demonstrated normal biventricular structure and function, with normal valves. No features of infarction, myocarditis, infiltrative processes, and arrhythmogenic cardiomyopathy were detected.

Electrophysiological study found normal atria-His and His-ventricular intervals, single atrioventricular nodal echoes only, and decremental atrioventricular and ventriculo-atrial conduction. No accessory pathway was demonstrated.

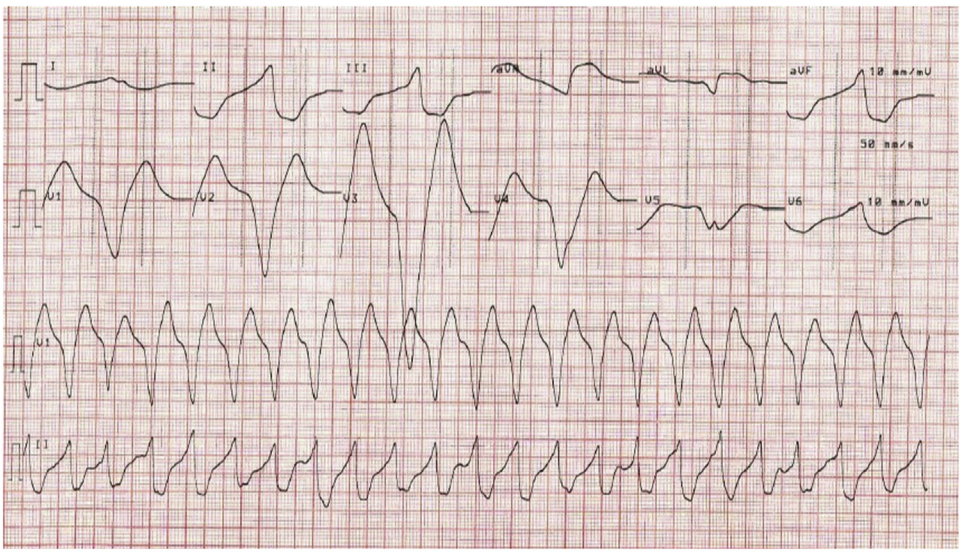
MANAGEMENT

Oral quinidine 200 mg 4 times per day (24.2 mg/kg/day) was commenced. On balance recommendation was that an implantable cardioverter-defibrillator (ICD) implantation should be offered if the patient

ABBREVIATIONS AND ACRONYMS

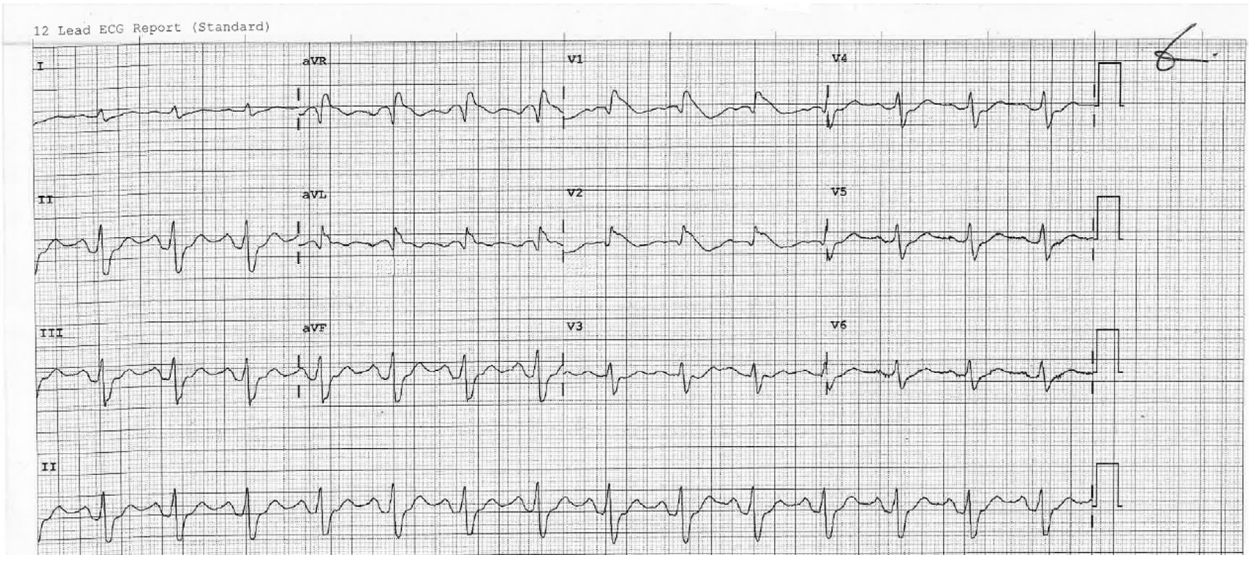
BrS = Brugada syndrome
ECG = electrocardiogram
ICD = implantable cardioverter-defibrillator
TCA = tricyclic antidepressant
VT = ventricular tachycardia

FIGURE 1 Initial Electrocardiogram



Initial electrocardiogram on presentation to hospital showing ventricular tachycardia with a ventricular rate of 134 beats/min.

FIGURE 2 Type 1 Brugada Pattern



Type 1 Brugada pattern on electrocardiogram following spontaneous reversion to sinus rhythm 10 min after initial admission.

had further BrS type changes on ECGs once amitriptyline had been stopped. However, it was also noted that her severe depression was only responsive to high doses of amitriptyline and that a pragmatic approach to protecting her in this context was discussed with the patient and her psychiatric team.

In addition to routine ICD counseling, the risk of poor wound healing from malnourishment was highlighted to the patient. The potential drug-induced nature of her BrS type changes was explained, as well as the uncertainty over whether future treatments or illnesses might provoke further VT. The patient was eager to proceed with ICD implantation and was deemed to have capacity to make this decision.

Multidisciplinary discussion recommended a transvenous single-chamber ICD, which was implanted during admission.

Following discharge without amitriptyline, ECG including high-right precordial leads showed a broad R wave in V1 and V2 suspicious for BrS, but not meeting criteria for a type 1 Brugada ECG (**Figure 6**). However, signal average ECG was abnormal in all 3 parameters.

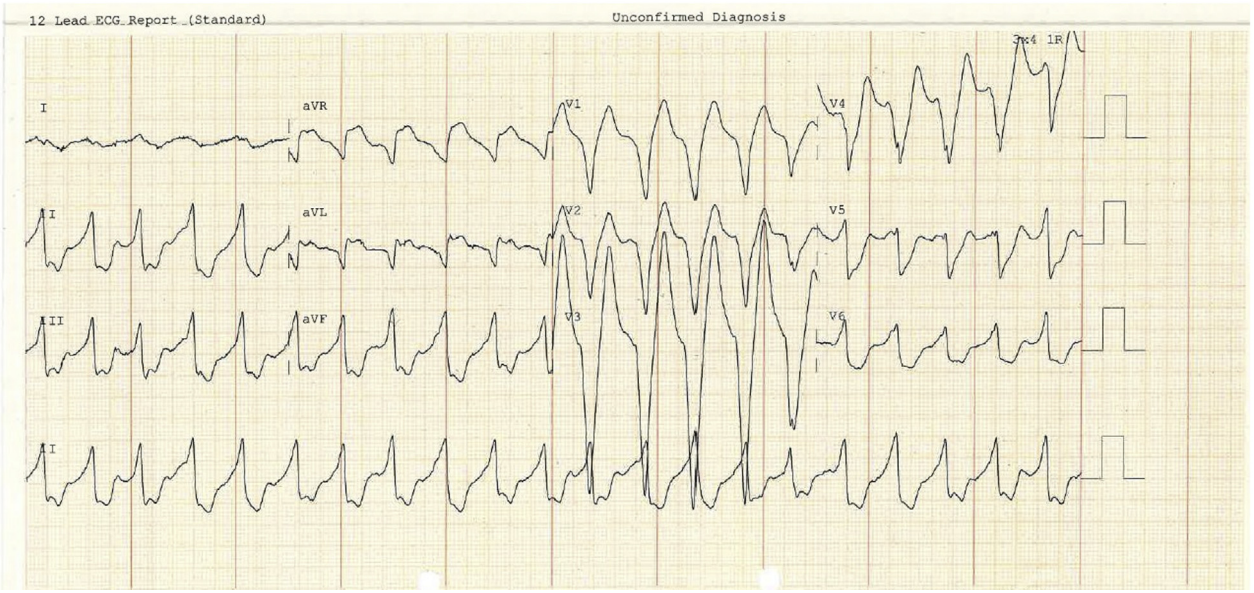
DISCUSSION

We present the first case of Brugada ECG with VT in the context of therapeutic amitriptyline. The possibility of amitriptyline toxicity cannot be definitively eliminated due to the absence of an amitriptyline level and significant individual variation in absorption and metabolism in context of a high dose for this patient's body weight. However, it is less likely that any true clinical features of toxicity were present at this level (7.6 mg/kg) because serious complications of tricyclic toxicity are more likely to be seen at >10 mg/kg (1).

Several Brugada phenocopy conditions exist and have gained recent prominence. Among the differentials are myocardial infarction with right ventricular involvement, electrolyte disturbance, pulmonary thromboembolism, accidental electrocution, congenital pectus excavatum (1), as well as adrenal crisis (2). The patient in question was not experiencing any of these conditions. It is to be noted that the patient had had a large meal prior to this clinical presentation and cases of characteristic Brugada ECG changes being unmasked by a large meal are well-documented. The underlying suggested mechanism is that of vagal tone modulation (3).

Tricyclic antidepressants (TCAs) are also known to produce Brugada-like ECG findings in up to 10% of overdose cases (4); of the 2 patients who died with ventricular fibrillation, only 1 had the Brugada type 1 ECG. TCAs are known to cause sodium channel blockade (5); these channels are key determinants of cardiac conduction and the reason for QRS prolongation in overdose. Following this, prolonged QRS

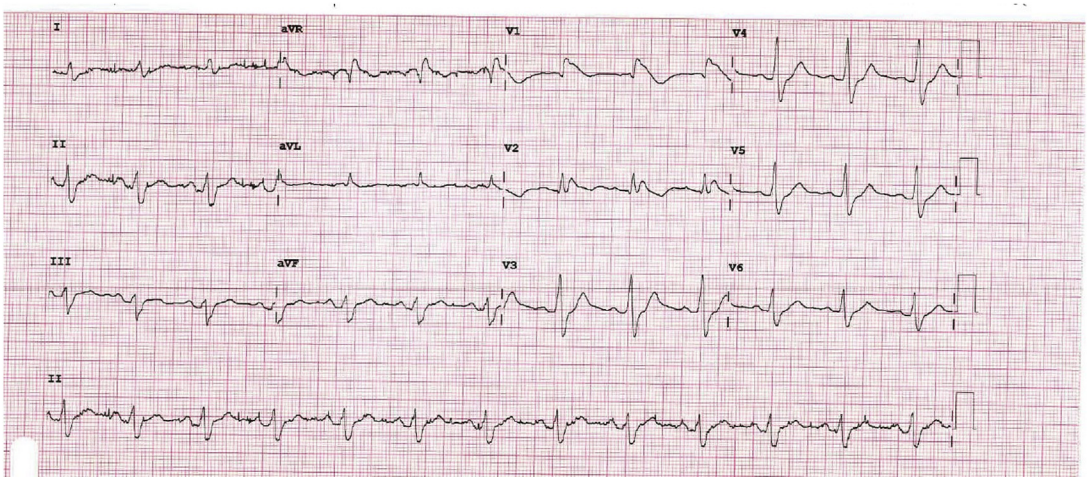
FIGURE 3 **Further Episode of Ventricular Tachycardia**



Further episode of ventricular tachycardia on electrocardiogram 8 h after initial admission.

was also noted to be a predictor of cardiological and neurological adverse events in TCA overdose (6). A study of 402 patients with intentional TCA overdose demonstrated type 1 Brugada ECG pattern in only 2.3% of patients, with no death due to ventricular arrhythmia (7). Amitriptyline is known to be a potentially arrhythmogenic drug (level IIa evidence); patients with BrS are counselled against using it. However, Brugada phenocopy at therapeutic dose has not been reported in a PubMed search. This is corroborated based on an animal study demonstrating that dose-dependent Brugada-like changes

FIGURE 4 **Sinus Rhythm on Electrocardiogram**



Sinus rhythm on electrocardiogram with further spontaneous Type 1 Brugada pattern.

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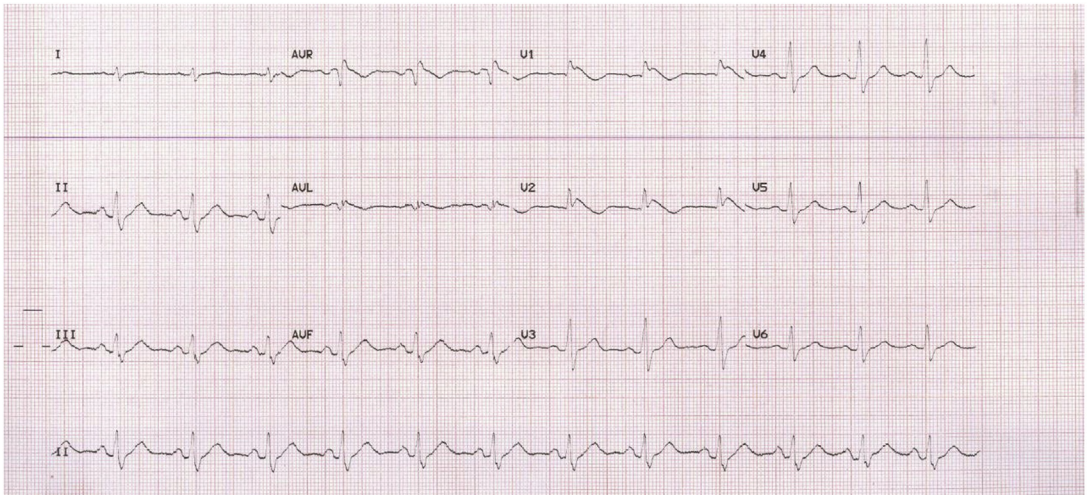
FIGURE 5 Type 1 Brugada Pattern on Electrocardiogram

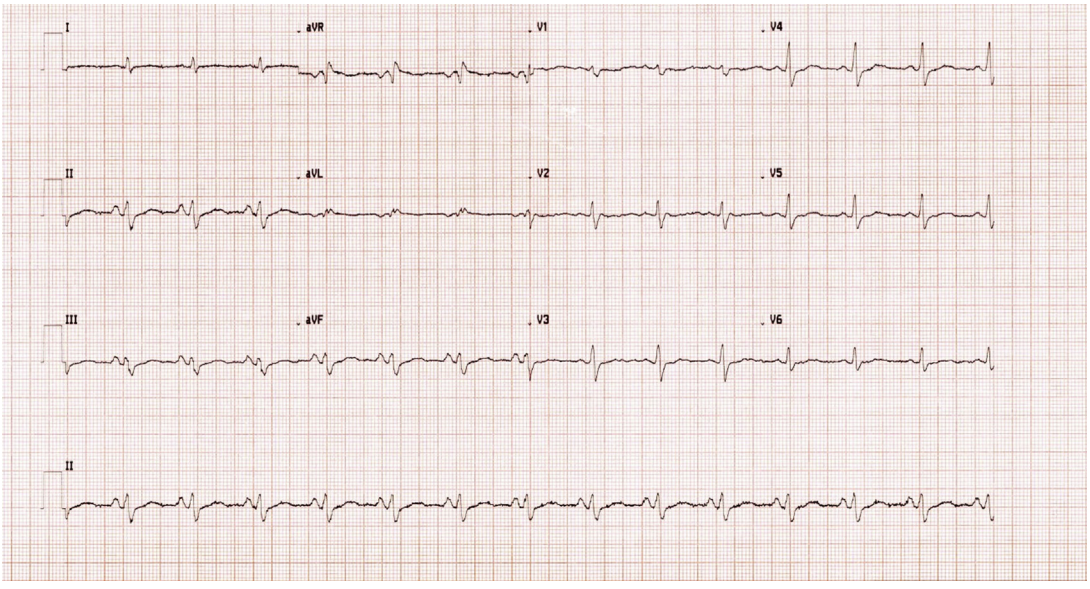


Type 1 Brugada pattern on electrocardiogram from 2016 during admission to emergency department.

are not present at normal therapeutic doses of amitriptyline (8).

Cardiac abnormalities, such as sinus bradycardia, reduced cardiac mass, and QT prolongation, in anorexia can recover following successful refeeding (9). Anorexia nervosa and BrS has been previously reported once, with the ECG pattern persisting after successful refeeding (10). This patient later proved to

FIGURE 6 Right Precordial Lead Electrocardiogram From Clinic Post-Discharge



Right precordial lead electrocardiogram from clinic post-discharge demonstrating broad R-wave in V_1 and V_2 suspicious for Brugada syndrome, but not meeting criteria for a type 1 Brugada electrocardiogram.

have a sodium channel, voltage-gated, type V, alpha subunit genetic mutation compatible with the diagnosis. The co-existence of BrS and seizures has been reported with interpretations ranging from co-existence (11,12) to Brugada-induced cardiac arrest mistaken for epilepsy (13). These examples showing true co-existence of BrS with anorexia nervosa or epilepsy demonstrate the need for vigilance over abnormal ECG signs rather than dismissal as phenocopies. Our patient's pathognomic ECG from 4 years prior to formal diagnosis underscores this assertion.

FOLLOW-UP

After her discharge back to the eating disorder unit her amitriptyline was restarted due to her severe and resistant mental health issues. She remains symptom-free on quinidine and has had no further ventricular arrhythmias detected by her ICD.

CONCLUSIONS

We describe type 1 Brugada ECG and VT in a patient on high doses of therapeutic amitriptyline in the context of low body weight. This case suggests the need to consider dose adjustment in underweight patients using amitriptyline. It also highlights the importance of careful ECG interpretation in the context of any seizure or collapse.

AUTHOR DISCLOSURES

Dr. Chow is supported by the Daniel Bagshaw Trust, UK (www.danstrust.org). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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