Sodium channelopathy with an overlap of Brugada syndrome, paroxysmal atrial fibrillation, and progressive cardiac conduction system dysfunction

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Introduction

Brugada syndrome is a rare diagnosis with a prevalence of 3–5 per 10,000, accounting for 4% of all sudden cardiac deaths (SCD). It can present with ventricular tachyarrhythmia and SCD in structurally normal hearts. The inheritance pattern is autosomal dominant. An electrocardiogram (ECG) showing a Brugada type 1 pattern with other clinical features is required for diagnosis. Different genes have been associated with the disease, the commonest being the voltage-gated sodium channel alpha type V gene (*SCN5A*).[1]

We report a 21-year-old male patient presented twice to the hospital from prison following being found in a collapsed status. The patient suffered cardiac arrest, and was resuscitated using an automated external defibrillator (AED), resulting in a return of spontaneous circulation. AED printouts were reviewed and showed ventricular fibrillation (VF). ECG showed atrial fibrillation (AF) with coved ST elevation in V_1–V_2 consistent with a Brugada-type 1 pattern (Figure 1). Reaching a correct diagnosis and consulting the appropriate experts led to the best possible outcome for the patient.

KEY TEACHING POINTS

- Detailed assessment of the electrocardiogram is essential in assessing patients presenting with transient loss of consciousness or syncope.
- Brugada syndrome is a rare channelopathy, with *SCN5A* loss-of-function being the commonest associated genetic abnormality.
- Atrial fibrillation is associated with Brugada syndrome and predicts a more adverse outcome.
- Quinidine exerts its antiarrhythmic effect by inhibiting transient outward K+ current.
- Implantation of an implantable cardiac defibrillator in aborted sudden cardiac death is a class 1 recommendation from the European Society of Cardiology

Case report

We present a 21-year-old male inmate with no past medical history of note and no family history of SCD, who had 2 hospital admissions following episodes of loss of consciousness. On the first admission, he was intubated, ventilated, and admitted to the Intensive Care Unit. A brain computed tomography was done, which was unremarkable, and he was treated for presumed meningitis based on positive blood culture. Drug and toxicology screening was requested to look for evidence of illicit drug use. The screening included synthetic cannabinoids, cannabis, amphetamine, benzodiazepine, cocaine, methadone metabolites, and opiates. All were negative, apart from benzodiazepine. A referral to the community adult psychiatry was suggested for suspected drug use/overdose.

On the second admission, a similar presentation of a sudden loss of consciousness was witnessed by his cellmate. Prison officers initiated cardiopulmonary resuscitation, and AED delivered 4 shocks, achieving return of spontaneous circulation. AED confirmed that the underlying rhythm was VF (Figure 2). He was admitted to the coronary care unit; Supplemental Figure 1 provides a flow chart describing our approach to diagnosing and managing this patient with recurrent transient loss of consciousness or syncope. Initial ECG showed AF with coved ST elevation in leads V_1 and V_2, compatible with the Brugada type 1 pattern. Repeated ECGs showed inferolateral J waves at the terminal portion of the QRS complexes and paroxysmal AF, compatible

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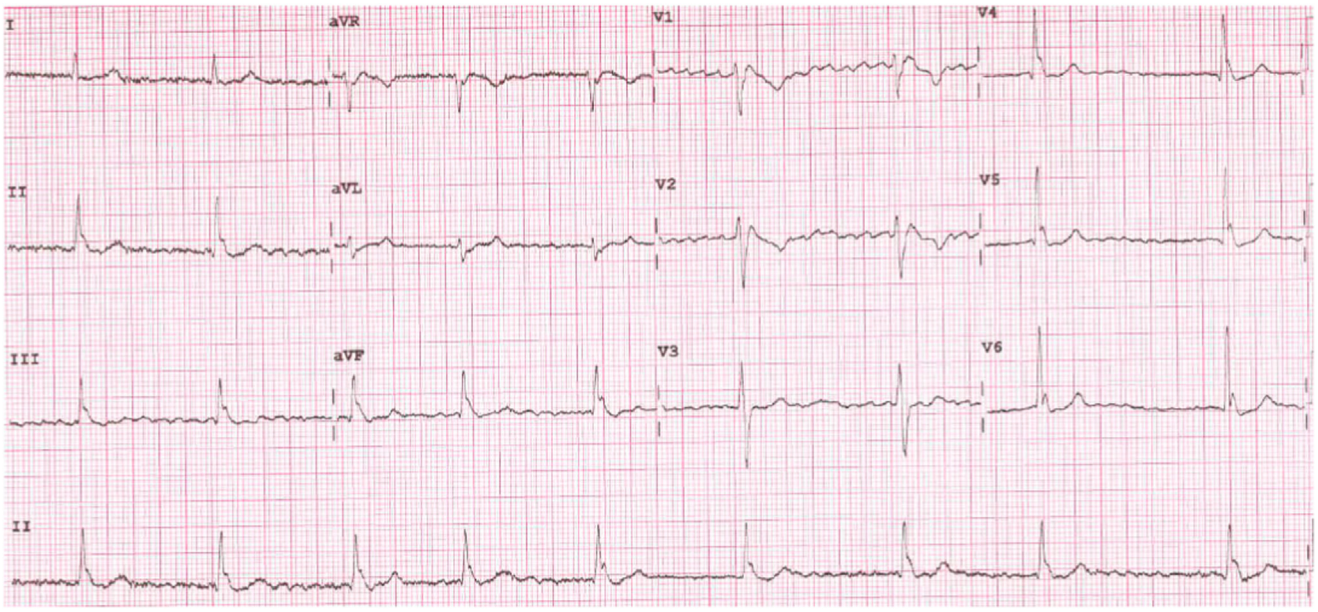

Figure 1 Electrocardiogram showing Brugada type 1 pattern changes with inferolateral J waves with atrial fibrillation.

with a sodium channelopathy overlap syndrome. An echocardiogram showed a structurally normal heart and blood tests were unremarkable.

In coronary care unit, he had 3 early-morning in-hospital VF arrests, requiring multiple shocks and treatment with intravenous amiodarone and beta-blockers. The ECG post cardioversion showed sinus rhythm with prolonged PR interval.

The patient was referred to the electrophysiology and inherited cardiac conditions team. Cardiac magnetic resonance imaging showed a structurally normal heart. He was first established on isoprenaline infusion, and the amiodarone and beta-blocker therapy were stopped; then he was transitioned to oral quinidine therapy, with excellent effect. The inferolateral J waves disappeared, and the quinidine-induced QT prolongation remained manageable around 470–480 ms. He also displayed evidence of atrioventricular (AV) conduction disease with PR prolongation of 260–280 ms initially and then further prolongation to 346 ms (Figure 3).

A dual-chamber implantable cardiac defibrillator (ICD) was implanted for secondary prevention of arrhythmic death. ICD was programmed as follows: Cut-off interval: VT 167 beats/min (360 ms), FVT 240 beats/min (250 ms), VF 200 beats/min (300 ms). Therapy VT = OFF; FVT therapy: ATP1 (type: Burst), ATP2 (type: Ramp), Shocks ×4 35 J. VF therapy: ATP during charging, Shocks ×6 35 J.

The patient was followed up in the inherited cardiac conditions clinic post discharge, with no further events. The PR interval was 200 ms, showing a hint of a type 1 Brugada pattern in lead V_1. A home monitor has not transmitted any therapies from the ICD, and ICD interrogation was satisfactory.

A 3-generation family history was taken, and there was no evidence of anyone else with cardiac issues or early sudden death. No genetic cause was identified on genomics laboratory report; the panel applied included *SCN5A*. The patient was advised not to drive for 6 months and must inform the Driver and Vehicle Licensing Agency. A discussion about the dangers of illicit drug use in causing arrhythmia in Brugada was made with the patient owing to his previous history of illicit drug use. He was also advised regarding over-the-counter medications and advised not to exercise alone.

Discussion

There is a difference between the Brugada pattern and Brugada syndrome. Asymptomatic patients with typical ECG findings and no other clinical features are said to have a Brugada pattern. On the other hand, those with typical ECG features with ventricular arrhythmias or SCD or associated clinical criteria are labeled as having Brugada syndrome.[2]

Factors such as mutations in the cardiac sodium channel *SCN* genes, right ventricle abnormalities, autonomic tone, fever, cocaine use, and some psychotropic drugs may contribute to the ECG changes and clinical manifestation of Brugada syndrome. For example, cocaine, neuroleptic drugs, and cyclic antidepressant overdose can block cardiac sodium channels, resulting in a transient Brugada ECG pattern.[2]

Mutations in *SCN* genes *SCN5A* and *SCN10A*, encoding a cardiac sodium channel's subunit, have been identified by genetic analysis. *SCN1B* mutations have been identified in Brugada syndrome probands. Reduction in sodium inflow currents owing to the defective myocardial sodium channel reduces the duration of normal action potentials. I(to), the transient outward current prominent in the right ventricle outflow tract epicardium, causes significant shortening of the action potential.[2]

Brugada syndrome was identified in 3%–24% of patients with idiopathic VF in a study by Remme and colleagues.[3]

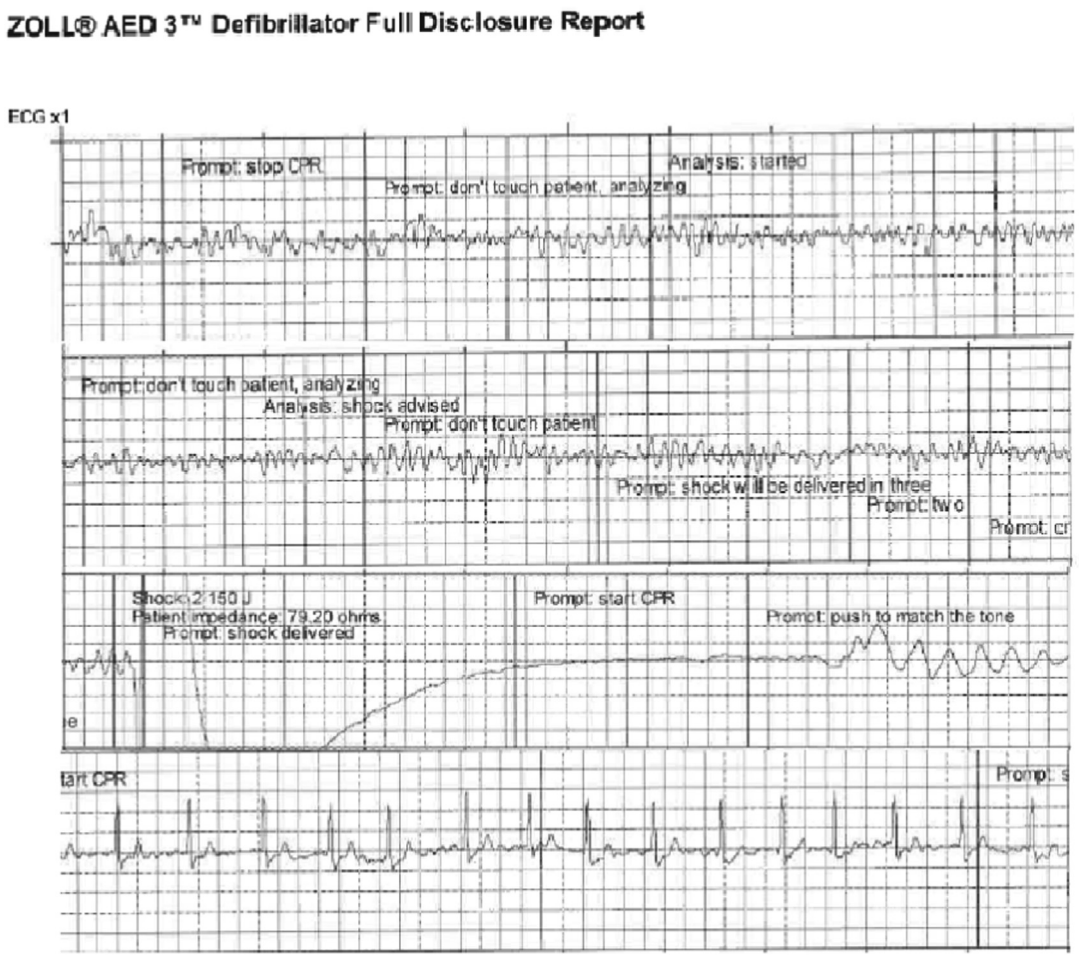

Figure 2 Automated external defibrillator traces during ventricular fibrillation and post shock. Postshock rhythm shows atrial fibrillation. CPR = cardiopulmonary resuscitation.

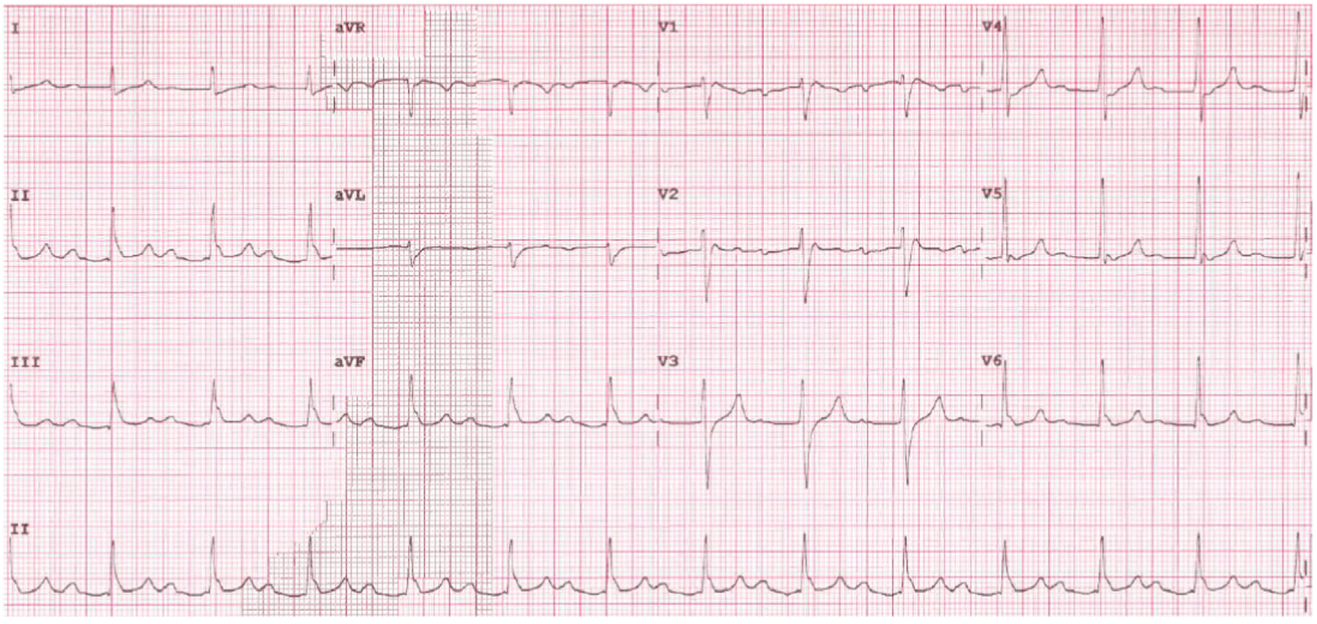

Figure 3 Electrocardiography showing PR prolongation – PR interval of 346 ms.

Almost 89% had documented VF during resuscitation by ambulance crew; 86% of patients had myocardial biopsies, which showed no evidence of structural heart disease; and some patients had ECG features of Brugada syndrome.[3] There is a male predominance, 2–9 times more likely in men. Men carry a greater risk than women, with a worse prognosis.[4–8] It is usually diagnosed in adulthood.

Atrial arrhythmias have been detected with Brugada syndrome, mostly AF. In 2 studies, by Bordachar and colleagues[9] and Kusano and colleagues,[10] 10%–20% of patients with Brugada syndrome had AF, associated with a higher risk of VF and a more severe disease process.

In a large study by Brugada and colleagues,[11] 547 patients with ECG suggestive of Brugada and no previous cardiac arrest were studied. Around 75% were male, with an average patient age of 41 years old. Brugada and colleagues concluded from the study that a higher risk of SCD was seen in patients with Brugada syndrome and no previous cardiac arrest. In patients who underwent programmed ventricular stimulation, sustained ventricular arrhythmia and a history of previous syncope were markers of poor prognosis. Absence of syncopal episodes, a diagnostic ECG after drug challenge, and noninducibility with ventricular stimulation was considered the lowest-risk group.

In another study, by Yan and Antzelevitch,[12] to demonstrate the cellular basis of Brugada syndrome, the authors identified that the trigger of ventricular arrhythmias could result from extrasystolic activity due to phase 2 re-entry arising in the intact wall of the canine right ventricle. Their data showed that medications that block I(to), such as quinidine and 4-aminopyridine, are proven effective.[12] This is compared to our case, where the J waves inferolaterally disappeared following quinidine initiation.

Drug challenge is sometimes required for patients with ECG changes suspicious for Brugada pattern or syndrome. The drugs usually used to unmask the ECG changes are sodium channel blockers such as ajmaline, flecainide, procainamide, or pilsicainide.[2] However, in our case, the diagnosis was made based on ECG findings, clinical presentation, and VF arrest; a drug challenge was unnecessary, and treatment with medications and ICD implantation was crucial.

Regarding pharmacological treatment, isoproterenol is considered helpful for treating electrical storms, the mechanism being a reduction in the QT interval by increasing rate.[13] As per the HRS/EHRA/APHRS expert consensus recommendation, ICD implantation is considered a class 1 recommendation for patients with Brugada syndrome who survived a cardiac arrest and or have spontaneously sustained VT with or without syncope. Class Ia antiarrhythmic drugs, such as quinidine, help prevent VF induction and help suppress spontaneous ventricular arrhythmias.[14]

Conclusion

This case describes a patient admitted following a successfully resuscitated VF arrest by cardiopulmonary resuscitation and AED defibrillation. The patient had a significant sodium channel disorder with evidence of Brugada, paroxysmal AF, and AV nodal conduction disorder with prolonged first-degree AV block. He was started on quinidine sulfate 600 mg twice daily and had a dual-chamber ICD fitted, and his ECG showed significant improvement with the help of medications.

The key point is that the ECG was not evaluated in detail following his first presentation; hence the diagnosis was missed. This is a reminder that one should approach the diagnosis and risk stratification of patients with transient loss of consciousness in a thorough and methodical manner, using the guidelines available.

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Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2023.06.004.

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