

Sudden death of a patient with epilepsy: When Brugada syndrome mimicry can be fatal



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Introduction

Brugada syndrome (BrS) is an inherited disorder characterized by coved-type ST-segment elevation in the right precordial leads and increased risk of sudden cardiac death (SCD) in ostensibly normal heart.¹ The electrocardiogram (ECG) manifestations may occur spontaneously or after the exposure to sodium channel blocking agents.² The main clinical manifestations (syncope and SCD) are caused by malignant ventricular tachycardia / ventricular fibrillation, which are related to an arrhythmogenic epicardial substrate located in the anterior aspect of the right ventricular outflow tract.^{3,4}

Idiopathic epilepsy and BrS share the pathophysiology of altered transmembrane ion current caused by mutations of ion channel subunit genes. Sodium channel dysfunction represents a common pathogenetic pathway for these 2 clinical entities that may be involved as a mechanism of sudden death. In addition, mutations of ion channel or arrhythmia-related genes are the most common defects found in patients experiencing sudden death in epilepsy.⁵

Coexistence of epilepsy and BrS in a family with *SCN5A* mutation has been reported, suggesting that sodium channel mutation may be responsible for cardiac and cerebral manifestations, probably at different ages in the same individual and/or in the same family.⁶ The latter underlines the importance of careful assessment of symptoms, detailed family history, and a thorough ECG analysis when evaluating patients with seizure-like symptoms.

Antiepileptic drugs (AEDs) are useful in controlling malignant neurologic manifestations, and their adjunctive use in refractory epilepsy reduces mortality 7-fold.⁷ On the other

KEY TEACHING POINTS

- Antiepileptic drugs may interfere with cardiac electrophysiology and expose vulnerable patients to potentially fatal arrhythmias.
- Syncope with tonic-clonic movements may be confused with epilepsy. A thorough cardiac evaluation is important before starting antiepileptic drugs.
- Suspicious symptoms, a family history of sudden death, and equivocal dubious electrocardiogram abnormalities are warning signs of an underlying arrhythmic disorder.

hand, a community-based study found an increased risk of SCD in patients with epilepsy treated with AEDs, and this risk was specifically associated with the use of sodium channel blockers.⁸

Among sodium channel blockers used as AEDs, phenytoin (which belongs to the IB class of antiarrhythmic drugs) has been described to induce a type 1 ECG Brugada pattern at supratherapeutic doses.⁹ However, its direct role as a trigger of a fatal ventricular arrhythmia in a patient with BrS has never been described.

Case report

The proband is a 36-year-old man of Italian origin with a family history of sudden death (father and paternal grandfather). He came to our clinic because of a previous episode of syncope without prodromes, showing a suspicious Brugada pattern on ECG. A transthoracic echocardiogram excluded structural abnormalities. The patient underwent an ajmaline challenge, which was stopped at 35 mg (ie, 50% of the full dose for the patient's weight) owing to the appearance of a typical type 1 Brugada pattern (Figure 1). Ventricular programmed stimulation was performed from the right ventricle

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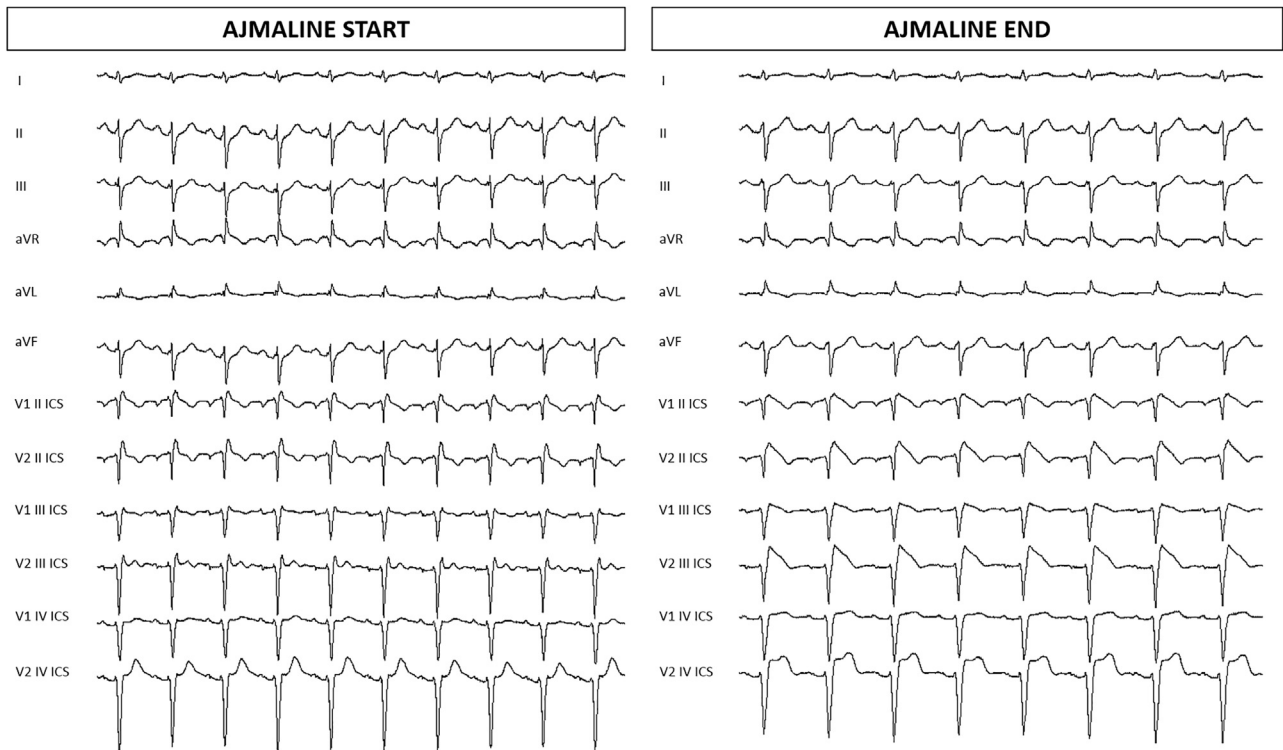


Figure 1 Proband's electrocardiogram (ECG) at baseline and after ajmaline challenge. Brugada pattern is evident after sodium channel blocker administration.

apex, which was negative for ventricular tachycardia / ventricular fibrillation inducibility. However, owing to the symptoms and family history, he was implanted with an implantable cardioverter-defibrillator in primary prevention.

The proband's family history, summarized by his mother, revealed that his paternal grandfather suffered from epileptic seizures, and he died suddenly at the age of 70. In addition, the proband's father died at the age of 65 years. He suffered from arterial hypertension and dyslipidemia, well controlled with adequate medical therapy. More recently before the fatal event, while still 65 years of age, this subject developed high fever (40°C) due to SARS-CoV-2 infection and asked his family doctor for intervention at home; the doctor diagnosed pneumonia and prescribed clarithromycin (1000 mg daily for 10 days). After 2 days, this patient experienced a syncope episode (associated with tonic-clonic movements and sphincter release), resulting in a sudden fall, which caused cranial trauma and a nasal bone fracture. He was admitted to the Emergency Department of the local hospital with high fever (40°C) and an unstable state of consciousness despite a good cardiac and respiratory function. A nasal swab confirmed SARS-CoV-2 infection. A cranial computed tomography scan excluded intracranial lesions and hemorrhage and reported the nasal bone fracture. Cerebrospinal fluid exam resulted negative for meningitis and other common infectious diseases affecting the central nervous system.

Of note, the 12-lead ECG during hospitalization (before the treatment with AEDs) clearly showed spontaneous type 1 Brugada pattern (Figure 2), in the absence of any electrolyte

imbalance or metabolic disorders at serial blood tests. Supportive measures and intensive care were provided, leading to progressive clinical improvement and complete neurological recovery.

According to the clinical presentation and family history, a diagnosis of epilepsy was made, and AEDs were prescribed. Phenytoin was administered at a dosage of 100 mg daily and the patient was instructed to undergo monthly neurological examination with serial checks of phenytoin blood levels. The first 2 consecutive controls were normal, and so the patient was advised to continue the established treatment.

The last crisis of syncope occurred at home, in the early morning, and was characterized by trismus, diaphoresis, and muscle rigidity. After this crisis, the proband's father was again taken to the emergency room of the local hospital. His ECG on admission is shown in Figure 3. He was diagnosed with ventricular tachycardia at 150 beats per minute, originating from the right ventricular outflow tract, causing hemodynamic instability, which was successfully treated by external DC shock.

Phenytoin blood levels were above the upper therapeutic window threshold, and recurrent ventricular arrhythmias were reported on the continuous ECG monitoring, requiring multiple external DC shocks. The patient was sedated, intubated, and admitted to the intensive care unit. On the same day an arrhythmic storm, relapsing despite multiple external DC shocks, resulted in hemodynamic decompensation and, eventually, the patient's death.

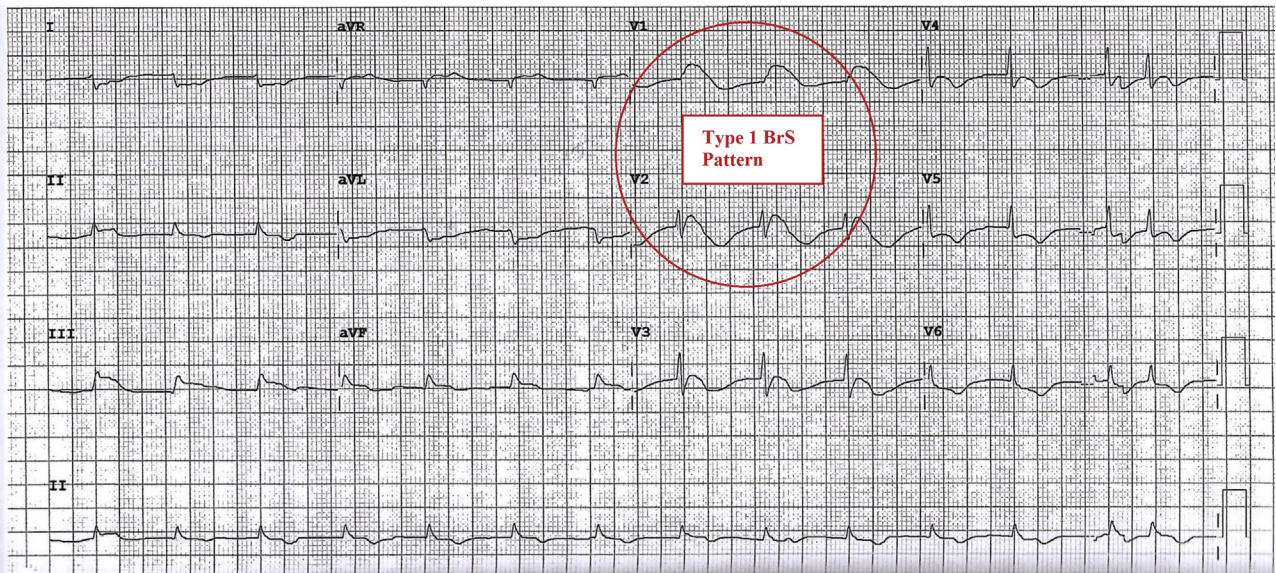


Figure 2 Proband’s father’s electrocardiogram (ECG) with spontaneous type 1 Brugada ECG pattern with ST-segment elevation in the inferior leads and T-wave abnormalities from V₄ to V₆.

Discussion

To our knowledge, this is the first report of arrhythmic death due to an overdose of an antiepileptic drug (phenytoin) in a patient with misdiagnosed BrS. An atypical clinical manifestation (seizure-like syncope), drug interference (phenytoin), and a wide arrhythmogenic substrate (spontaneous type 1 ECG Brugada pattern) resulted in a perfect storm leading to a tragic outcome.

BrS is recognized as a relevant cause of life-threatening ventricular arrhythmias and SCD among individuals with structurally normal hearts. Epilepsy can be associated with both cardiac arrhythmias and an increased risk of SCD. Uncontrolled epilepsy results in alterations of cardiac

electrophysiology, potentially leading to arrhythmias owing to ictal discharges in brain regions controlling sympathetic and parasympathetic tone or life-threatening abnormalities of cardiac repolarization.¹⁰ Non-seizure-related arrhythmias have also been observed in patients with epilepsy, which can be life-threatening and manifest as sudden cardiac death.¹¹ The role of AED in these circumstances is controversial and debated. In a community-based study, AED use was associated with an increased risk of SCD, and specifically with the use of sodium channel blocker agents.¹¹

The susceptibility to SCD in epilepsy might be the consequence of a shared genetic cause with arrhythmogenic syndromes. Indeed, both BrS and idiopathic epilepsy are

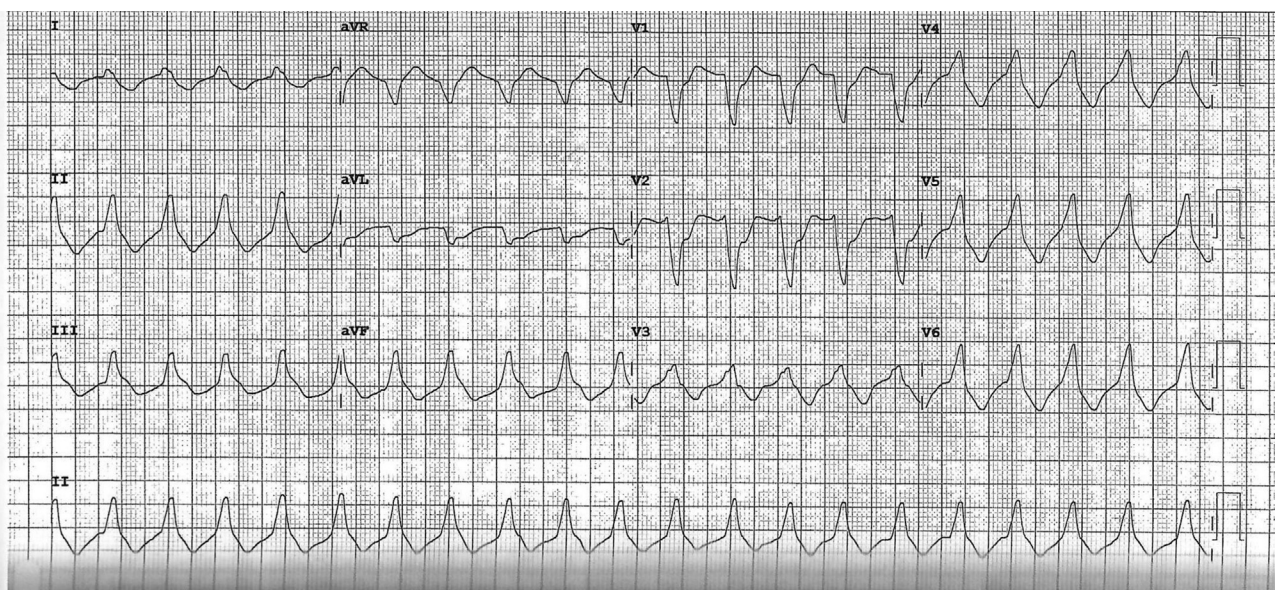


Figure 3 Proband’s father’s electrocardiogram showing ventricular tachycardia.

associated with heterozygous mutations in ion channel genes. The role of channel dysfunction in the pathogenesis of cardiac arrhythmias and epilepsy is well known, as variants of the cardiac sodium channel (ie, *SCN4A*, *SCN5A*, *SCN10A*, and *SCN11A*), gated potassium channel (ie, *HCN1*), and calcium channel (ie, *EFHC1* and *CACNA1A*) are frequently documented.^{12,13} The most clinically relevant mutations are those affecting the voltage-gated sodium channel, which are expressed in various tissues and are involved in various clinical manifestations: brain (epilepsy), heart (cardiac arrhythmias), skeletal muscle (myotonia and periodic paralysis), peripheral nervous system (pain disorders).¹⁴

Epilepsy and cardiac arrhythmias can be confused in the early stages of the diagnostic process when a syncope occurs as the first clinical manifestation. Once considered specific to epileptic phenomena, generalized tonic-clonic movements during loss of consciousness are commonly reported in cardiac syncope as well. This overlap in clinical manifestations can lead to misdiagnosis of life-threatening cardiac conditions and, as occurred in this case, to prescription of potentially harmful drugs.

Phenytoin can elicit type 1 Brugada ECG pattern at supratherapeutic blood levels,⁹ but its proarrhythmic effect has never been documented. Phenytoin is a first-generation anti-epileptic and a class IB antiarrhythmic drug used for the treatment of epilepsy. It acts by blocking the voltage-dependent sodium channels and, because of this particular activity, may exacerbate the voltage gradient between endocardium and epicardium, which could be lethal in BrS patients. Sodium channel blockade in a patient with BrS can lead to spontaneous, sustained ventricular arrhythmias, refractory to external cardioversion, resulting in cardiocirculatory collapse, as also reported by our group.^{15,16}

Conclusion

This case report demonstrates the deleterious effect of phenytoin administration in a patient with BrS, whose predisposing condition was initially overlooked. Patients with seizure-like events should always be carefully evaluated by a cardiologist to rule out an underlying condition, especially

if a neurologic etiology is not clearly established. In cases of suspicious symptoms, a family history of sudden death, and/or equivocal dubious ECG abnormalities, a sodium channel blocker test should be performed before initiating a specific drug treatment.

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