case report

# Brugada syndrome: an unusual cause of syncope in a young patient

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Syncope is a sudden and transient loss of consciousness associated with loss of postural tone from which recovery is spontaneous.[1] The most common cause of syncope in the general population is neurocardiogenic followed by primary arrhythmias.[2] In the presence of underlying heart disease, syncope is associated with a high rate of mortality.

Sudden cardiac death (SCD) is a witnessed cardiac arrest within 1 hour after the onset of acute symptoms or unexpected, un-witnessed death in a patient known to have been well within the previous 24 hours.[3] It occurs with an approximate incidence of 1 per 1000 inhabitants per year in the West.[4] The leading cause of SCD is ventricular fibrillation secondary to either acute ischemic events or underlying structural heart disease. However, no identifiable cause could be found in 10% of these victims during autopsy or during extensive evaluation of surviving cases.[4]

Brugada syndrome is a new clinical entity first described by Brugada and Brugada in 1992.[5] This syndrome is responsible for approximately 4% of all SCD and 20% of SCD in patients without structural heart disease.[6] It is now considered an important cause of syncope among young patients.

## CASE

A 19-year-old male laborer, previously healthy, presented to our emergency department due to sudden loss of consciousness and falling down after emotional stress. This lasted for few seconds as described by his companion who witnessed the event. There was a history of brief palpitation, but he denies any chest pain, shortness of breath or seizures. The patient retained consciousness rapidly, without headache or confusion, but could not recall the event exactly. He reported no similar attacks before, and had no family history of syncope, epilepsy, or sudden unexplained death.

On examination the patient was a young, well-built and healthy male. His blood pressure was 137/82 mm Hg, heart rate was 124 beats per minute and he had a regular respiratory rate 16 breaths per minute and temperature of 36.8°C. The heart, chest, abdomen and lower limb examination were normal. Neurological evaluation showed no focal deficit. The electrocardiogram showed sinus tachycardia, right bundle branch block pattern, and coving type ST-segment elevation in the precordial leads V1, V2 and V3, which is characteristic of Brugada syndrome type 1 (Figure 1A).

The patient was hospitalized and investigations showed a normal creatinine kinase, troponin I, prolactin, a negative toxicology screen, and other routine laboratory tests were normal. X-rays, electroencephalogram and echocardiography were also within normal ranges. He was monitored at the Coronary Care Unit for four days. The ST segment elevation on the ECG returned to normal on the second day. No arrhythmias were reported during this period, but he was stratified in the high-risk group for future arrhythmias.

A cardioverter defibrillator was implanted and he was discharged from the hospital 2 days later. He was followed up at our outpatient clinic after 6 days, at which time the ECG was normal (Figure 1B) and the patient was free of symptoms. He was seen again 3 months later due to viral pharyngitis and was asymptomatic but his ECG showed fever-induced ST-segment elevation in V1 (Figure 1C).

## DISCUSSION

Brugada syndrome is a type of cardiac membrane channelopathy. The overall prevalence among the normal population is not established because the ECG is dynamic and there are concealed forms of this syndrome.[7] Some studies report its prevalence to be about 0.05% to 0.6%.[8,9] However, this prevalence is higher in south Asia than in Europe and the United States.[10]

Brugada syndrome is a familial disease. About 60% of patients with Brugada syndrome have a family history of sudden death or have family members with the

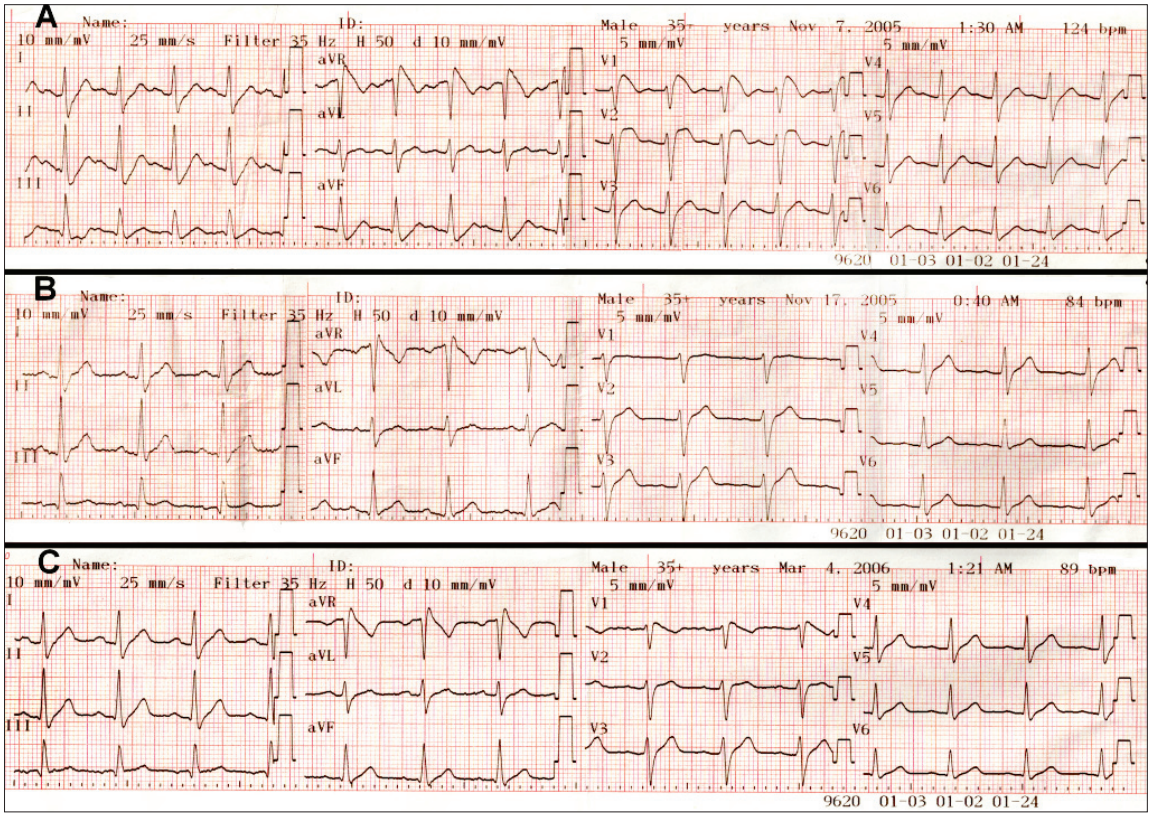


**Figure 1.** (A) The characteristic ECG of Brugada syndrome. (B) During follow-up. (C) During febrile illness.

ECG pattern of Brugada syndrome. Forty percent of patients have sporadic de novo mutations.[11] It is inherited as autosomal dominant disease with variable penetrance. Chen and coworkers described the genetic nature of the disease and its association to a mutation in the cardiac sodium channels.[12] About 80 mutations have been linked to the gene SCN5A.[13-16]

The exact electrophysiologic mechanisms of this syndrome are not fully understood. Prominent transient outward potassium current (Ito) in the right ventricular epicardium results in marked shortening of the duration of the action potential causing a voltage gradient within the endocardium which results in the ST elevation on the ECG. The voltage gradient may result in reexcitation (phase 2 re-entry) of the epicardium, which triggers ventricular arrhythmias. The sodium current (INa) opposes the potassium current (Ito) during phase 1 of the action potential. The faster inactivation of the sodium channel or the lack of function caused by the mutation explains why an unopposed current (Ito) becomes prominent and markedly shortens the duration of the action potential at the epicardial level.[17]

Patients with Brugada syndrome may be asymptomatic and diagnosed accidentally, or present with syncope. Unfortunately, in some patients, SCD might be the first presentation of the disease. It usually manifests during adulthood with a male predominance (male to female ratio, 8:1). The mean age of sudden death in victims of Brugada syndrome is about 35 to 40 years.[11] All clinical manifestations of Brugada Syndrome are attributed to ventricular tachyarrhythmias and their complications. Mostly, these arrhythmias occur at rest or during nighttime.[11]

Brugada syndrome is diagnosed, after exclusion of structural heart disease, when there is a documented history of one of the electrocardiographic or clinical events (Table 1) in association with a type 1 ECG pattern.[6] These ECG changes are variable over time, depending on the autonomic interaction and the administration of antiarrhythmic drugs.[18] Our patient fulfilled the diagnostic criteria for Brugada syndrome and needed no further invasive diagnostic tests. As he developed syncope, he most likely developed VT/VF that terminated spontaneously, which is a common presentation in Brugada syndrome.

There are three ECG patterns used to diagnose Brugada syndrome. All have a J-wave amplitude ≥2 mm. Type 1 is characterized by the coving type ST-seg-

ment elevation in the precordial leads V1, V2 and V3, followed by T wave inversion. Type 2 shows a saddleback ST-segment elevation in leads V1, V2 and V3, but the downward displacement of the ST-segment lies between the two elevations of the segment but does not reach the baseline and the T-wave could be positive or biphasic. Type 3 shows the same saddleback ST-segment as in type 2, but touches the baseline and the T-wave is always positive.[19]

The presence of a type 1 ECG pattern in asymptomatic patients is sufficient to diagnose this syndrome in the absence of other temporary conditions that may provoke ECG patterns that mimic Brugada syndrome (Table 2). The pharmacologic provocation test is not indicated in these patients as it has neither diagnostic nor prognostic values yet.[19,6] However, genetic testing is recommended to support the clinical diagnosis, and for early detection of relatives at potential risk.[6] On the other hand, in patients with type 2 and 3 ECG patterns, the drug challenge test is recommended to clarify the diagnosis. It is considered positive if type 2 or 3 converted to type 1, while conversion of type 3 to type 2 after the drug challenge is considered inconclusive.[19]

The normal resting ECG is not sufficient to exclude the presence of Brugada syndrome, especially in family members of a patient with this syndrome or patients with unexplained syncope. Therefore, the drug provocation test is recommended. It can be done by administering a sodium channel blocker like ajmaline, flecainide, procainamide or pilsicainide under intensive monitoring conditions. The test is considered positive if there is an additional 1-mm ST-segment elevation in the right precordial leads V1, V2 and V3.[20] Placement of the right precordial leads in a superior position in the second intercostal space can increase the sensitivity of the ECG for detecting the Brugada phenotype in some patients with or without administering sodium channel blockers.[21]

Contrary to the fact that vagal stimulation and bradycardia increase ST-segment elevation in Brugada syndrome, and that adrenergic stimulation or tachycardia decrease or may even normalize the ST-segment elevation,[22] our patient developed syncope after a stressful condition, which is characterized by sympathetic overstimulation. His ECG showed the characteristic ECG of Brugada syndrome while his heart rate was 125 beats per minute. On the other hand, there is growing evidence that Brugada syndrome is unmasked by fever,[23] which was noted in our patient.

Brugada syndrome is now considered different from arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) in both its clinical presentation and genetic predisposition.[19] Drug challenge may be useful in discriminating between the two diseases.[24] While Brugada syndrome and sudden unexpected death syndrome (SUDS) are the same entity, they share a lot of genetic, clinical, electrocardiographic and prognostic properties.[10]

The list of drugs that can cause Brugada-like ST-segment elevation is expanding. These drugs include some antiarrhythmic, antianginal, psychotropic and addiction drugs, but it is not known if there is a genetic predisposition for these patients.[6]

Programmed electrical stimulation (PES) reproducibility induces VT or VF in almost all Brugada syndrome patients with a history of aborted sudden death or syncope.[25] But, shall we extend the electrophysiological testing to the family members and asymptomatic patients? Despite the belief that the inducibility of VT/VF in electrophysiological studies may stratify asymptomatic patients with Brugada syndrome into the high-risk group,[26] and mandates the need for implantation of implantable cardioverter defibrillator (ICD), other

**Table 1.** Electrocardiographic and clinical events complicating Brugada syndrome.

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| • Documented ventricular fibrillation |
| • Polymorphic ventricular tachycardia |
| • Family history of sudden cardiac death |
| • Coved-type ECGs in family members |
| • Inducibility of ventricular tachycardia with programmed electrical stimulation |
| • Syncope |
| • Nocturnal agonal respiration |

ECG: electrocardiogram

**Table 2.** ECG abnormalities mimicking Brugada syndrome.

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| • Atypical right bundle-branch block |
| • Left ventricular hypertrophy |
| • Early repolarization |
| • Acute pericarditis |
| • Acute myocardial ischemia or infarction |
| • Pulmonary embolism |
| • Prinzmetal angina |
| • Dissecting aortic aneurysm |
| • Central and autonomic nervous system abnormalities |
| • Duchenne muscular dystrophy |
| • Thiamin deficiency |
| • Hyperkalemia |
| • Hypercalcemia |
| • Arrhythmogenic right ventricular dysplasia/cardiomyopathy |
| • Pectus excavatum |
| • Hypothermia |
| • Mechanical compression of the right ventricular outflow |
| • Well-trained athletes |
| • Cocaine intoxication |

**Table 3.** Treatment options for patients with Brugada syndrome.

| Clinical | Family History | ECG | EPS | Treatment |
|---|---|---|---|---|
| Symptomatic | - | - | - | ICD |
| Asymptomatic | - | - | Inducible VT/VF | ICD |
| Asymptomatic | Positive | Spontaneous | Negative | ? ICD |
| Asymptomatic | Negative | Spontaneous | Negative | Observation |
| Asymptomatic | Negative | Drug-induced | Negative | Observation |

ECG: electrocardiogram, EPS: electrophysiologic study, VT/VF: ventricular tachycardia/fibrillation.

studies failed to support this hypothesis.[27-29] Brugada and coworkers found that inducibility of sustained ventricular arrhythmias during PES is a powerful predictor of outcome in Brugada syndrome.[30,31] They concluded that symptomatic patients require protective ICD implantation because of the high incidence of arrhythmic events, independent of the results of the PES, for which the test could simply be avoided. Asymptomatic patients can be reassured if they are non-inducible,[31] while asymptomatic patients with positive PES should undergo ICD implantation.[32] So, EPS is recommended in all asymptomatic patients with Brugada syndrome.

Implantation of cardiac defibrillator is the only effective intervention for preventing sudden cardiac death in Brugada syndrome.[25] It is recommended for all symptomatic patients. Although repeated episodes of polymorphic ventricular tachycardia can be treated with isoproterenol or quinidine,[11,33] other antiarrhythmic drugs do not protect against sudden cardiac death in Brugada syndrome.[11] Indications for ICD are summarized in Table 3.

Brugada syndrome is associated with a high prevalence of malignant arrhythmias and sudden death. The presence of Brugada ECG by itself is a risk for arrhythmic events, and normalization of the ECG during follow up does not indicate a better prognosis.[17] Patients with spontaneous Brugada ECG and a history of aborted sudden cardiac death or syncope are at highest risk for development of these arrhythmias.[16] Asymptomatic individuals with spontaneous Brugada ECG are also at high risk for arrhythmic events if sustained ventricular arrhythmias are induced during EPS, while asymptomatic patients have a benign prognosis if the EPS is negative.[32]

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