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CASE REPORT

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# Cascade screening can be life-saving: a family with multiple cases of brugada syndrome and sudden cardiac death

Parham Ghafouri[1,2], Sarah Taaghi[3*], Ala Keykhavani[4], Ali Bozorgi[5] and Abolfath Alizadeh diz[6]

## Abstract

Brugada syndrome (BrS) may cause a spectrum of symptoms from asymptomatic patients to those who experience cardiac arrest and sudden cardiac death. The diagnosis is confirmed after observation of type I Brugada pattern on the electrocardiogram. Following the diagnosis, risk stratification can help select therapeutic options. Cascade screening should be started to find other family members with BrS. We present a 41-year-old woman diagnosed with BrS, and cascade screening of her relatives unveiled a pedigree of BrS among their family.

**Keywords** Brugada syndrome, Challenge test, Arrhythmia, Sodium channel blocker, Flecainide

## Introduction

Brugada Syndrome (BrS) is an inheritable cardiac channelopathy, mainly characterized by a particular electrocardiogram (ECG) pattern consisting of coved-typed J point elevations > 0.2 mV in ≥ 1 right precordial leads with T wave inversions in the absence of cardiac structural abnormalities [1]. Patients with BrS are more amenable to ventricular arrhythmia/fibrillation (VA/VF) and sudden cardiac death (SCD). As far as 20% of SCD cases with structurally normal hearts happen in BrS patients [2]. Family history of SCD in close relatives has been reported in about 26% of cases, and numerous genes are involved in the pathogenesis of BrS [1, 3] Although an autosomal dominant mode of inheritance has been reported, incomplete penetrance and variable expressivity may be the results of a complex of multiple genetic and environmental factors that control the BrS pattern of inheritance [4]. Nevertheless, after the diagnosis of the disease in a patient, all first-degree relatives should undergo screening as 67% of cases may be asymptomatic [5]. Here, we describe a woman who experienced palpitation and chest tightness while admitted for acute kidney injury (AKI) and had multiple relatives with a history of SCD under 45 years of age.

## Case presentation

A 41-year-old woman (proband IV-B), a known case of type 2 diabetes mellitus, hypertension, asthma, and chronic kidney disease (CKD) with a biopsy-proven diagnosis of chronic tubulointerstitial nephritis, was admitted to our center due to nausea, vomiting, and increased serum creatinine levels (creatinine = 5.3 mg/dl). Baseline creatinine levels were about 1.5–2 mg/dl. Under the impression of AKI on CKD, she was admitted to the nephrology ward. She did not complain of fever, frequency, dysuria, urine color change, or

*Correspondence:
Sarah Taaghi
Drsarahtaaghi@gmail.com
[1] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2] Students' Scientific Research Committee (SSRC), Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Cardiology, School of Medicine, Hazrat-E Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran
[4] Department of Cardiology, Hazrat-E Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran
[5] Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran
[6] Department of Cardiology, Rajaei Heart Center, Iran University of Medical Sciences, Tehran, Iran

hematuria. However, she reported oliguria. She had stable hemodynamics and her physical examination was unremarkable, without any signs of asterixis and alterations in the level of consciousness.

A cardiology consult was requested due to a sudden episode of palpitation and chest tightness. The episode lasted for 10 min and ended spontaneously. ECG after the termination of palpitation showed atypical right bundle branch block, coved-type J point elevation > 2 mm in the right precordial (V1-V3) leads with gradually descending ST segment and T wave inversion.

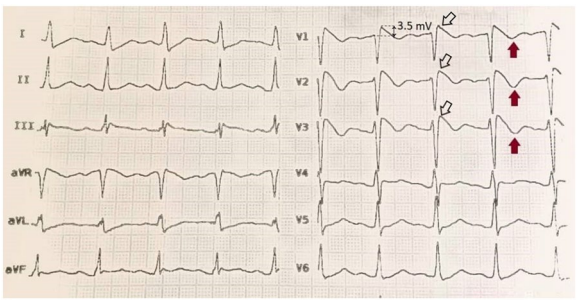


**Fig. 1** ECG of the index case after episode of palpitation and chest discomfort; in V1-V3, leads coved-type 3.5 mV J point elevation (white arrows) and T wave inversions (red arrows) are compatible with type I Brugada ECG pattern

This ECG pattern was compatible with the spontaneous type-I Brugada pattern (Fig. 1).

First, we ruled out Brugada phenocopies, like hyperkalemia, hypercalcemia, acidosis and RVOT ischemia. Cardiac troponin I levels were checked twice, and both came out negative (< 0.04 ng/mL). Simultaneous potassium and calcium levels were 3.9 and 9.2 mEq/L, respectively, and venous blood gas showed normal pH. On transthoracic echocardiography, she had a left ventricular ejection fraction of 60% with no signs of structural or regional wall motion abnormalities.

With detailed history taking, she recalled an episode of palpitation followed by syncope two months ago. Also, she mentioned several relatives with a history of sudden cardiac death under 45 years of age; her brother (IV-A), her uncle (III-C), and her cousin (IV-I). Furthermore, her grandfather and her great uncles all died at the age under 45 (Fig. 2).

All her siblings and paternal relatives were screened with 12 leads ECG and detailed history taking. They had normal ECGs and were asymptomatic except for one of her sisters (proband IV-C), who experienced multiple episodes of palpitation and pre-syncope in the past three months. Since day-to-day variability in ECG presentation may hinder the diagnosis [6], we performed a provocative test with a sodium channel blocker on her siblings and her father and put them under close surveillance. After obtaining baseline ECG

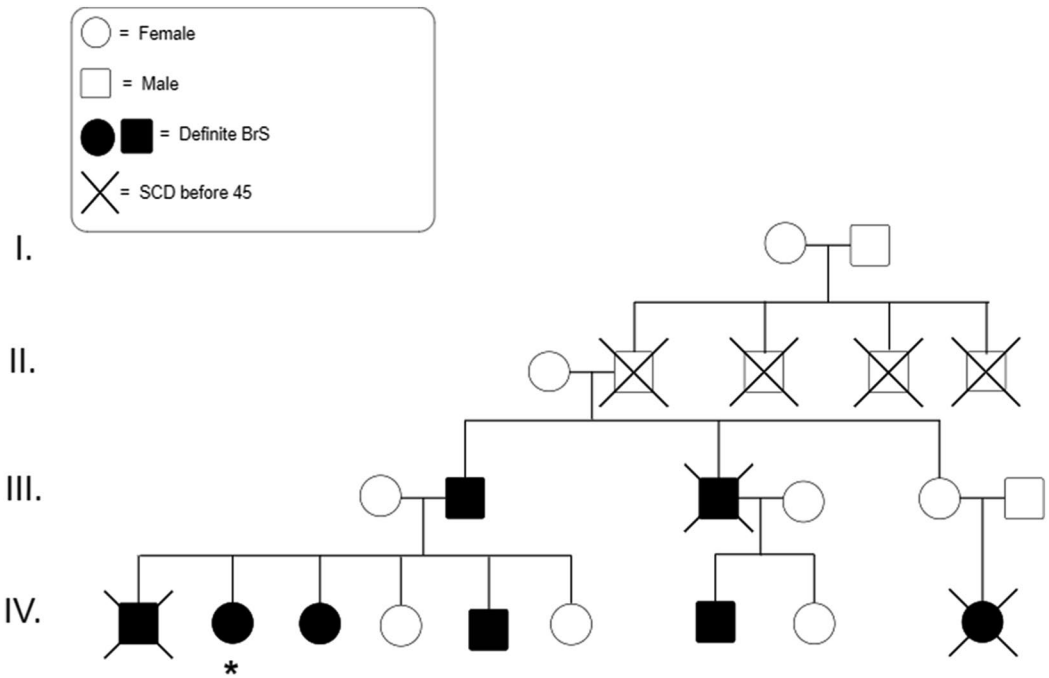


**Fig. 2** The pedigree of the family; the index case (proband IV-B) is distinguished with *. BrS: Brugada syndrome, SCD: sudden cardiac death

with higher placing of V1 and V2 leads, 400 mg oral flecainide was administrated. Serial ECGs were taken every 15 min for an hour and then each hour for the next 8 h. For her sister (proband IV-C), after two hours, V1 and V2 leads began to change, and in the 4th hour, the ECG was compatible with Brugada type-I (Fig. 3). Furthermore, her father and her brother had ECG changes compatible with Brugada type-I during provocative drug challenge test.

Among her cousins, one of them (proband IV-G, 25 y/o) had spontaneous type-I Brugada pattern, but he was asymptomatic. We managed to find his father's ECG and medical records. He had a spontaneous Brugada type-I pattern as well!

A subcutaneous implantable cardioverter defibrillator (sICD) was implanted for her and her sister since they were symptomatic (Fig. 4). Also, because of his spontaneous type-I ECG pattern and strong family history of SCD, ICD was implanted for her cousin.

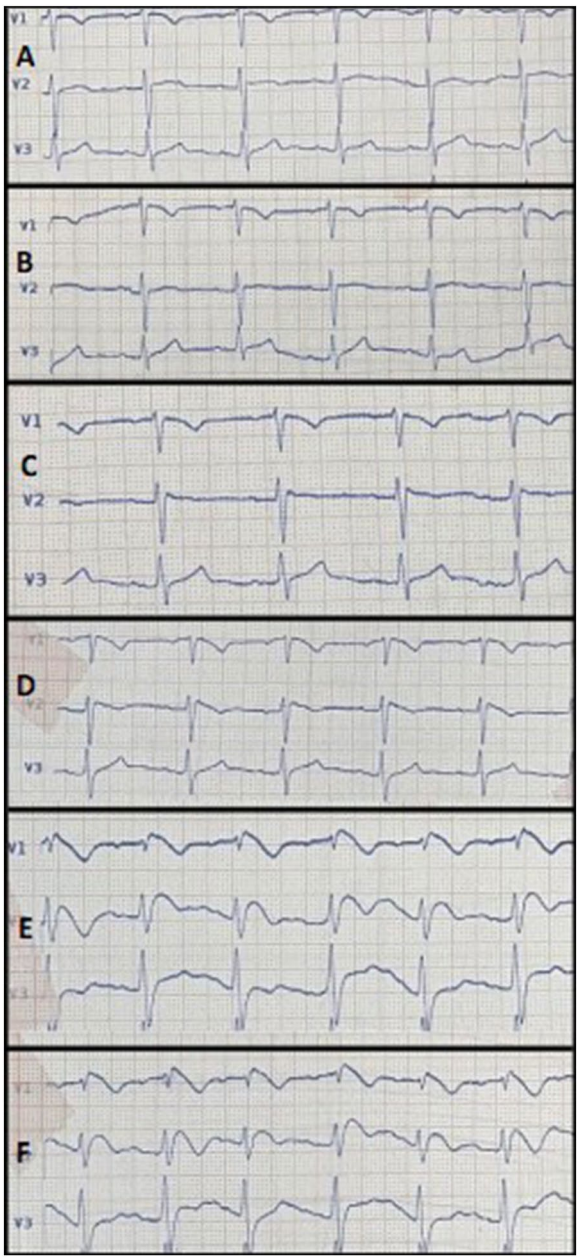


**Fig. 3** Provocative challenge test with 400 mg oral flecainide. V1 and V2 leads were placed higher, in the 2nd intercostal space and serial ECG at **A** baseline; **B** 15 min; **C** 1 h; **D** 2 h (ST segments in V1 and V2 are changing); **E** 4 h (type I Brugada ECG pattern can be seen); and **F** 5 h after administration of flecainide

## Discussion

Approximately two third of BrS patients do not experience any symptoms [5] and many are unaware of their disease until symptoms such as syncope or aborted cardiac arrest happen that require immediate medical intervention. BrS increases the risk of VA/VF and is responsible for 4–12% of all SCDs [2]. Thus, timely diagnosis and proper management could be life-saving. A family history of BrS in close relatives might be a diagnostic clue and initiates a screening cascade leading to early recognition of other family members with BrS. In this study, after diagnosing BrS in a 41 y/o woman and further investigating her relatives, we found a pedigree of BrS in an Iranian family.

Although BrS is considered a genetic cardiac arrhythmia syndrome with an autosomal dominant inheritance pattern, mutations are only found in about 35% of cases [4]. Mutations in *SCN5A,* which encodes the alpha subunit of cardiac $Na^+$ channels ($Na_v1$, 5), affect 30% of cases

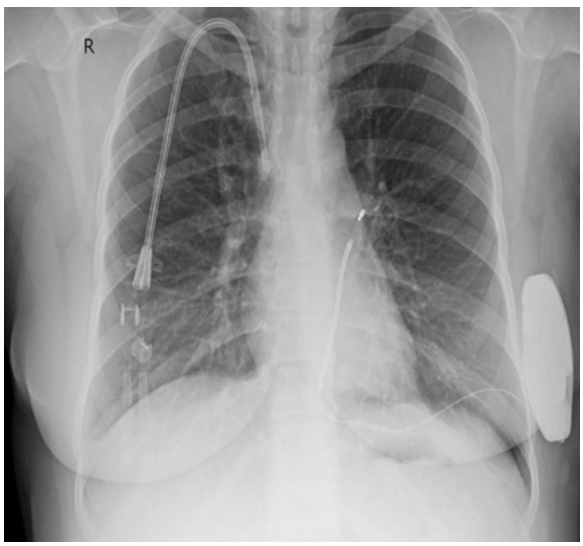


**Fig. 4** Posterior-anterior chest X-ray view after implantation of subcutaneous implantable cardioverter defibrillator for proband IV-B

and a definite association exists between BrS and *SCN5A* mutations [4]. Other mutations in sodium, potassium and calcium channels are responsible for the pathogenesis of BrS in 5% of cases. Besides, even in the known cases with mutations of *SCN5A,* incomplete penetrance and variable expressivity lead to diverse phenotypes in family members with the same mutations [7, 8]. A recent study has demonstrated that mutations in the cholesterol- and fibrosis-related genes caused more severe phenotypes in patients with mutations of ion channels [8].

The prevalence of BrS is 8–10 times higher in men than women. Furthermore, men experience arrhythmic events at earlier ages and have more severe phenotypes [9]. The effect of sex hormones and differences in the expression of cardiac transmembrane channels are supposed to be responsible for gender differences in BrS [1, 10]. Similarly, in this family, more men were affected (7 men versus 3 women). Men had severe phenotypes, as 6 of them died from SCD. Also, we observed that patients of the same gender experienced different clinical symptoms confirming the variable expression of BrS.

According to a recent definition of the disease [11], in the absence of Brugada phenocopies, the diagnosis is mainly confirmed with coved ST-segment elevation $\geq 2$ mm in $\geq 1$ lead in the right precordial leads V1, V2, occurring either spontaneously or after provocative drug test with sodium channel blockers. Thus it is crucial to rule out Brugada phenocopies at first, as they can mimic Brugada ECG pattern [12]. Pharmacological challenge could diagnose suspected cases without a spontaneous type-I ECG pattern [13]. Provocative test should be performed in an inpatient setting, and the test should be withheld as soon as type-I ECG pattern appears. After the diagnosis was established in proband IV-B, cascade family screening began. The provocative test was performed on her family members which led to the diagnosis of BrS in three of them.

Three main therapeutic options for BrS are ICDs, radiofrequency ablation and pharmacological therapy. In symptomatic patients who experienced aborted cardiac arrest, VA/VF, or frequent episodes of syncope, ICD implantation is recommended as the first line of therapy and has been shown to reduce mortality in this population [13]. However, because of inappropriate shocks and device-related complications, the decision to implant an ICD requires further risk stratification. sICD may be a suitable alternative in younger patients as it has fewer lead-associated complications. sICD was implanted for our case and her sister regarding their history of syncope and ECG pattern.

The most challenging issue in this family was whether to implant an ICD for proband IV-G. Asymptomatic patients with spontaneous type-I ECG pattern experience a low but significant arrhythmic events rate of 0.8% per year [5]. Current guidelines lack recommendations regarding device-based therapies in this population [13]. A recent study based on a decision-analytical simulation model showed that ICD-based approaches had higher quality-adjusted life years (QALY) and prevented more cardiac arrests compared to observation [14]. Furthermore, they showed that in individuals under 35 years old, upfront ICD maximized QALY compared to ICDs guided by electrophysiologic studies (EPS) [14]. Besides, the inducibility of VA/VF on EPS did not predict higher rates of VA/VF or ICD shocks in this population [15]. Altogether his family history of SCD convinced us to directly implant ICD for him without further risk stratification with EPS.

In conclusion, we described an Iranian family with multiple cases of BrS and SCD. The authors suggest that with detailed history taking and cascade screening of families with BrS patients, clinicians should find asymptomatic cases and take timely actions to avoid malignant arrhythmic events and SCD. Also, we encourage other researchers to further validate the prognostic value of scoring systems for selecting therapeutic options in BrS patients, especially asymptomatic patients.

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**Author contributions**
PG and ST designed and formed the study conception. ST collected the clinical data of the patients. PG wrote the body of manuscript. ST, AK, AB and AA reviewed the draft critically. All authors read and approved the final version of the manuscript.

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**Availability of data and materials**
Data and material are presented within the manuscript.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
A written informed consent was obtained from all the patients for the use of potentially identifiable images or other health information contained in our submission. Also, all the patients are aware of its use and the context of such use. We understand that it is our responsibility to have secured this permission and maintain the security of such personal health information. We confirm that a copy of the consent form is available for review by the Editor upon request.

**Competing interests**
The authors declare no conflicts of interest. We declare that we are employees of Iran University of Medical Sciences (S.T., A.K. and A.A.) and Tehran University of Medical Sciences (A.B) which are government institutions and their primary functions are medical education, medical research, medical treatment and primary health care services. Also, we declare that our manuscript is being

submitted by the authors that "none "of them are official representatives of the government.

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