

A 33-year-old man after sudden cardiac arrest as a first manifestation of Brugada syndrome (RCD code: V-1A.1)

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Abstract

Brugada syndrome is an autosomal dominant genetic disease with variable expression characterized by abnormal electrocardiographic findings – right bundle branch block and ST-segment elevation in the anterior precordial leads, without evidence of structural heart disease. Individuals affected by the disease have an increased risk of ventricular tachyarrhythmias and sudden cardiac death (SCD). We present a case of a 33-year old man who was admitted to cardiology department after sudden cardiac arrest due to ventricular fibrillation. Evaluation for a structural heart disease was negative and routine tests did not reveal the cause of cardiac arrest. Retrospective evaluation of the patient electrocardiograms showed changes consistent with Brugada type 2 pattern that were variable over time. Performed pharmacological challenge with sodium channel blocker – ajmaline – provided an ambiguous result. Nevertheless, the patient was qualified for an implantable cardioverter defibrillator implantation as a secondary SCD prophylaxis. He underwent the procedure without complications and was discharged home in good general condition without symptoms. *JRCD 2016; 2 (7): 1–1*

Key words: rare disease, electrocardiography, ajmaline challenge, ventricular arrhythmias, implantable cardioverter-defibrillator

Case presentation

A 33-year old man was admitted to cardiology department after sudden cardiac arrest due to first-ever ventricular fibrillation (VF) (Figure 1) and after successful resuscitation spend next eighteen days in intensive care unit (ICU). Cardiac arrest occurred at home, in sitting position, while watching television. It was not preceded by exercise, trauma or stress. Patient did not recall any alarming symptoms occurring before the event. Resuscitation was immediately started by his father and afterwards continued by ambulance team. Return of spontaneous circulation was achieved after two defibrillations. In the following period, during ICU hospitalization the patient developed respiratory failure and pneumonia, probably secondary to the aspiration of gastric content. Moreover, status epilepticus with recurrent tonic-clonic seizures was observed. Laboratory tests on admission drew our attention to relatively low blood potassium level (3,7 mmol/l). Due

to the increased blood d-dimer concentration (1886,93 ng/ml, reference range <500 ng/ml) and respiratory failure, there was suspicion of pulmonary embolism, however computed tomography pulmonary angiography did not reveal any emboli in pulmonary arteries. Blood levels of cardiac troponin I and the MB fraction of creatine kinase (CKMB) were slightly increased without a dynamic pattern characteristic for myocardial infarction (MI). During the hospitalization neurological disorders were ruled out based on two CT and magnetic resonance imaging exams of the brain and electroencephalography, which did not show any significant abnormalities. After six days of ICU treatment the patient regained consciousness, and on physical exam did not present any neurological deficits. After clinical stabilization the patient was transferred to our department for further evaluation and treatment.

Prior to this event he hadn't had any chronic diseases and he hadn't been using any medications. He had no history of drug use or alcohol abuse. On admission he didn't present any cardiac-related

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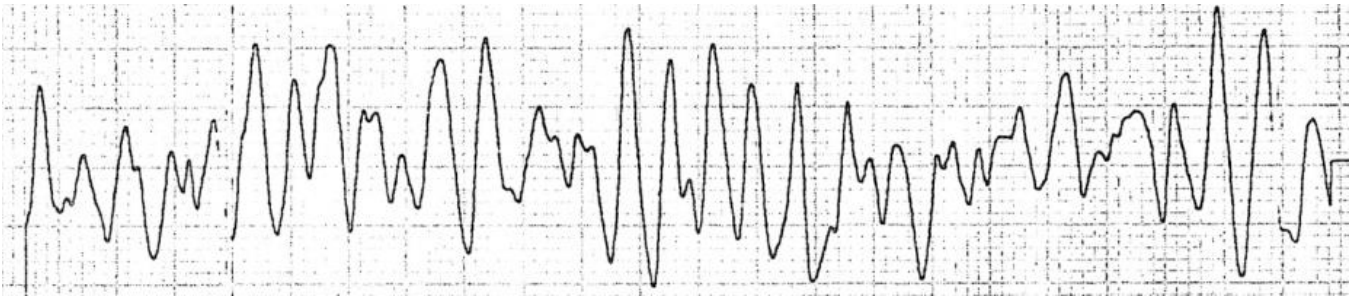


Figure 1. Electrocardiogram taken by the ambulance team during cardiac arrest showing ventricular fibrillation

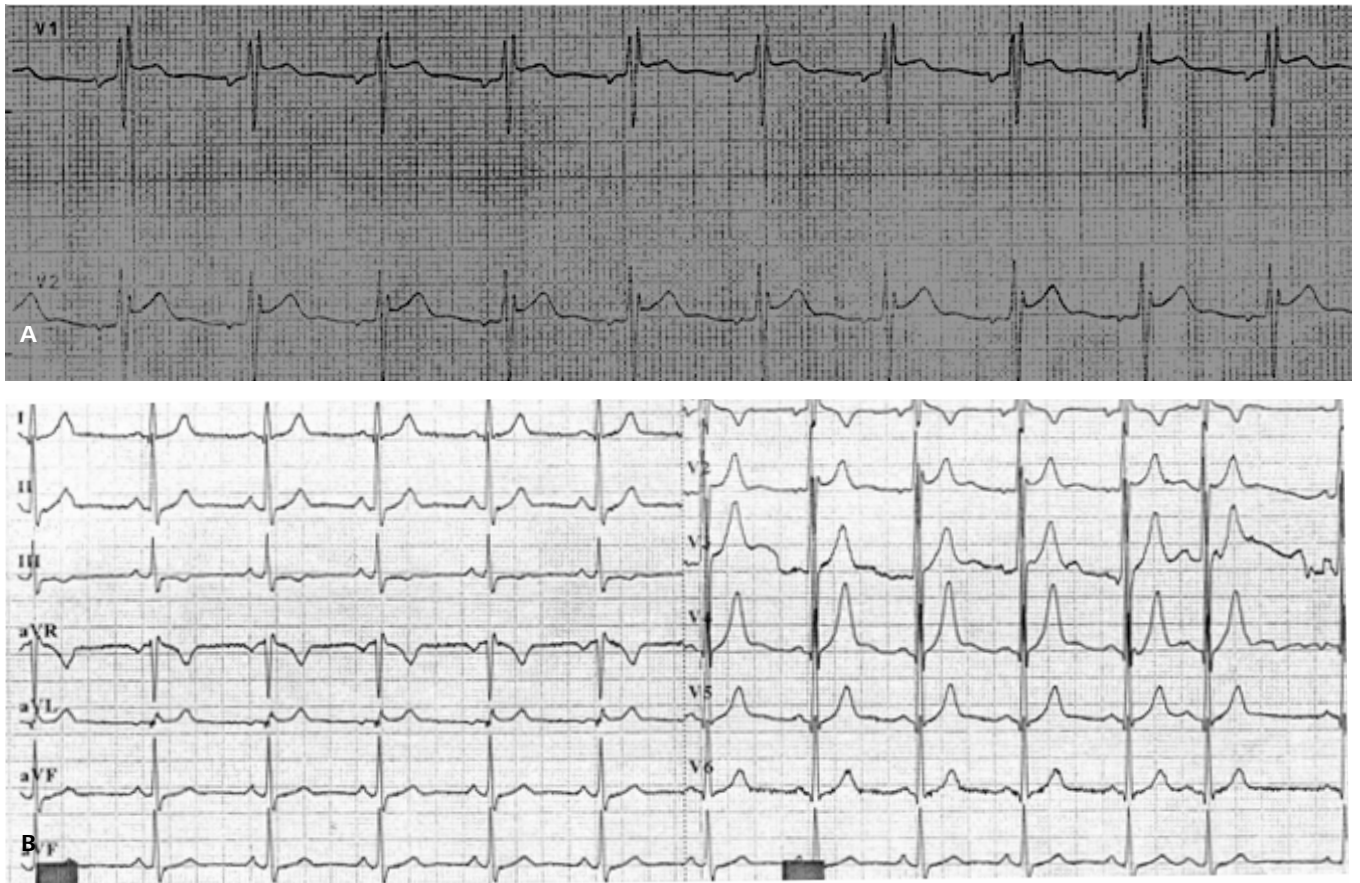


Figure 2. Retrospective evaluation of previous electrocardiograms performed during hospitalization at ICU revealed variable over time findings consisting of a right bundle branch block and ST segment elevation in leads V1 to V2 consistent with Brugada type 2 pattern (a, b). The ST segment had a “saddle back” ST-T wave configuration, including ST segment elevation descending towards the baseline, with upright (a: leads V1, V2; b: lead V2) or negative (b: lead V1) T wave

symptoms, he had no history of angina, palpitations, syncope and he reported good exercise tolerance. Furthermore, he had no family history of sudden cardiac death (SCD) but his father underwent MI at the age of 60. On admission to our department the patient had good general appearance, his vital signs were normal. The physical exam was unremarkable.

Laboratory testing on arrival showed normocytic anemia (hemoglobin 12,7 g/dL, mean corpuscular volume 88,0 fL). Other laboratory tests including cardiac high-sensitivity troponin T, CK-MB, total serum creatinine kinase concentration, N-terminal brain natriuretic peptide concentration and C – reactive protein were

within the reference range. A standard 12-lead electrocardiogram (ECG) showed sinus rhythm with heart rate of 84 beats per minute.

Retrospective evaluation of the patient’s ECGs obtained during the ICU hospitalization revealed several findings that were variable over time (Figure 2). They included right bundle branch block (RBBB) with QRS duration of 120 milliseconds (ms) and ST segment elevation in leads V1 to V2 consistent with Brugada type 2 pattern. The ST segment had a “saddle back” ST-T wave configuration, including ST segment elevation descending towards the baseline, with negative (lead V1) or upright (lead V2) T wave.

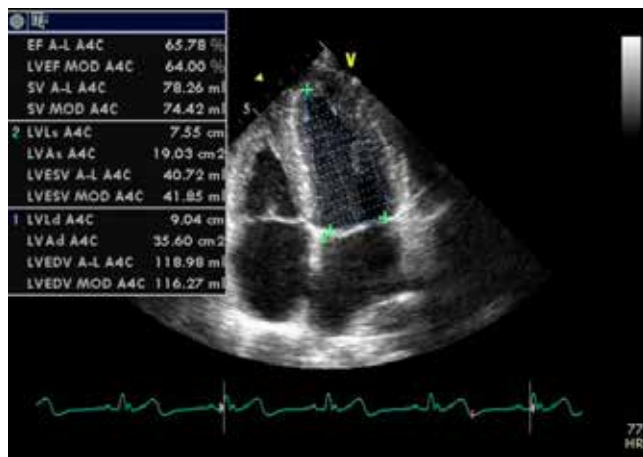


Figure 3. Transthoracic echocardiography. Normal global systolic function of the left ventricle with ejection fraction of 66% and with no segmental wall motion abnormalities

QT interval duration was 360 ms and corrected QT interval (with Bazett's formula) was 418 ms.

Transthoracic echocardiographic study showed normal global systolic function of the left ventricle with ejection fraction (EF) of 66% without segmental wall motion abnormalities. The size of the heart chambers were within normal range. There were no echocardiographic signs of right ventricular dysfunction or pulmonary hypertension, nor significant valvular diseases or pericardial effusion (Figure 3). Chest radiograph, Doppler ultrasound of carotid and vertebral arteries as well as ECG Holter monitoring for 24 hours also showed no abnormalities.

Further evaluation for structural heart disease was carried out with cardiovascular magnetic resonance imaging. Heart chambers were not enlarged, systolic function of both ventricles as well as their walls thickness were normal (end diastolic volume (EDV) – 143 ml, end systolic volume (ESV) – 57 ml, mass -142 g; right ventricle: EF – 59%, EDV-147 ml, ESV-60 ml, mass – 47 g). The study did not reveal areas of late enhancement or characteristics typical for arrhythmogenic right ventricular cardiomyopathy.

Additional tests were performed to establish the possible diagnosis of Brugada syndrome. Drug challenge with sodium channel blocker (ajmaline) was performed. Patient was given ajmaline intravenously at a dose of one milligram per kilogram of body weight. While performing the test, there repetitive standard 12-lead ECGs were obtained following 1 hour after drug administration and afterwards the patient had continuous ECG monitoring for 24 hours. During that time he didn't report any discomfort or symptoms, there were no arrhythmias or systemic blood pressure drop observed. 1-millimeter ST segment elevation in V1 lead 3 minutes after ajmaline administration and 5-millimeter ST segment elevation in V2 lead 17 minutes later were observed. However, characteristic type 1 Brugada ECG pattern wasn't exposed by a sodium channel blocker challenge (Figure 4).

Discussion

Definition

The Brugada syndrome is an autosomal dominant genetic disorder with variable expression characterized by abnormal electrocardiographic findings and an increased risk of ventricular tachyarrhythmias and SCD. Patients present with RBBB and minor ST-segment elevation in the anterior precordial leads, without evidence of structural heart disease [1]. It is important to recognize the difference between Brugada pattern and Brugada syndrome. Those terms, have been used to describe patients with the mentioned typical ECG findings and are distinguished by the presence or absence of clinical symptoms of ventricular tachyarrhythmia.

There are two distinct patterns of ST elevation [1,2,3]:

- The classic Brugada type 1 electrocardiographic pattern, which is also referred to as the “coved type” Brugada pattern, presents ST segment elevation (≥ 2 mm) which descends with an upward convexity to an inverted T wave.
- The type 2 pattern, referred to as “saddle back” Brugada pattern, consists of ST-T wave configuration, in which the elevated ST segment descends toward the baseline, then rises again to an upright or biphasic T wave.

The 2015 European Society of Cardiology (ESC) Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [4] provide definition for Brugada syndrome. Recommended (class I, level C) criteria are as following: ST-segment elevation with type 1 morphology ≥ 2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the second, third or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium channel blockers.

Epidemiology

The prevalence of Brugada syndrome ranges from 1 in 1000 to 1 in 10 000 and varies depending on the population, with higher morbidity in Southeast Asia than in Western countries [5]. It shows age- and sex-related penetrance. The Brugada pattern is nine times more common in men than in women [6]. Mechanisms of this phenomenon are unclear, but animal models suggest that there may be an impact of testosterone on cardiomyocytes outward potassium current [7]. VF in the course of the disease occurs at a mean age of 41 ± 15 years. It is typically observed during rest or sleep [8]. Factors like fever, excessive alcohol intake and large meals are known to be triggers unmasking the type I ECG pattern and predisposing to VF [5]. It was shown in a meta-analysis that the incidence of arrhythmic events (sustained ventricular tachycardia or fibrillation or appropriate implantable cardioverter defibrillator (ICD) therapy or SCD) in patients with Brugada syndrome reached 13,5% per year in patients with a history of previous aborted sudden cardiac arrest. On the other hand the frequency of these events in asymptomatic patients was 1% per year [9]. In 30–50% of individuals who die suddenly because of documented or suspected Brugada syndrome, SCD was the first manifestation of the disease [10].

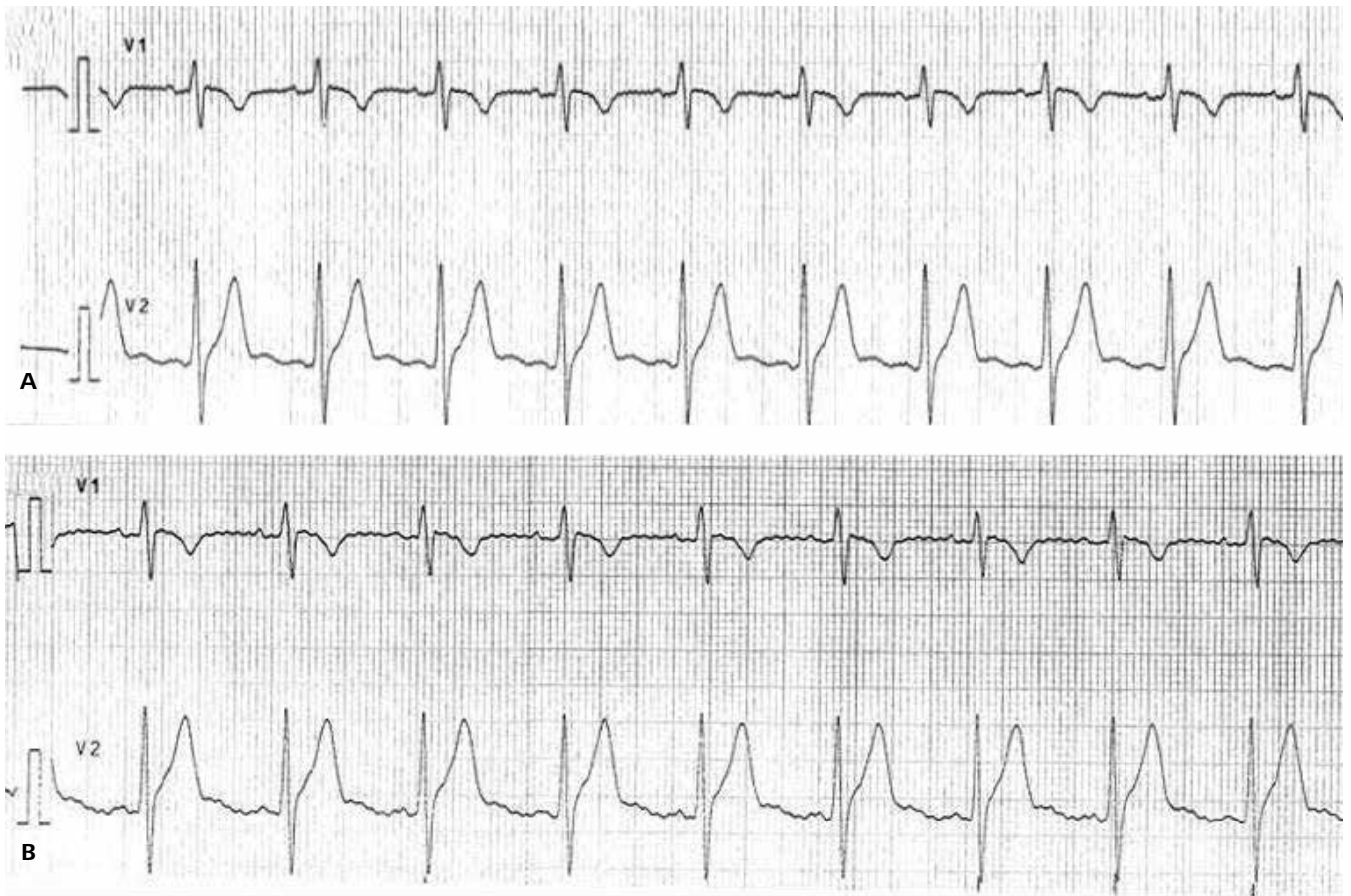


Figure 4. Drug challenge with sodium channel blocker was performed. There occurred 1-milimeter ST segment elevation in V1 lead 3 minutes after Ajmaline administration and 5-milimeter ST segment elevation in V2 lead 17 minutes later. Type 1 Brugada ECG pattern wasn't exposed by a sodium channel blocker challenge

Etiology

Brugada syndrome has a vast spectrum of clinical presentation – from completely asymptomatic to SCD as the first manifestation of the disease. What exactly determines the clinical presentation is unknown. The ECG manifestations of Brugada syndrome only reflect a multitude of possible etiologies [11]. There have been identified multiple mutations linked to the disease. The most common are mutations affecting pore-forming cardiac sodium channel subunits, coded by genes *SCN5A* and *SCN1B* [12,13]. In an international compendium of mutations in the *SCN5A* gene there were found 293 different mutations in 2111 unrelated individuals. Mutations were confirmed in 10- 20% of the patients [14]. The *SCN5A* gene is only one of 12 different genes involved in Brugada syndrome [11]. Other mutations that decrease the sodium channel current have been identified, like in glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*) trafficking of the sodium channel [15]. In patients with clinical diagnosis of Brugada syndrome mutations in the alpha and beta subunits of the calcium channel gene also have been found [16].

Gene mutations associated with Brugada syndrome cause reduction or loss of sodium or calcium current in combination with altered functional properties of voltage-gated sodium channels [17]. That results in heterogeneous loss of action potential dome during

the plateau phase in the right ventricular epicardium, which leads to a marked dispersion of repolarization and refractoriness and the potential for phase 2 reentry [18].

Still, only in 30% of families with proven Brugada syndrome, abnormalities in germinal cells are found [11]. Currently there are three different theories trying to identify patomechanism of the disease: – (1) the depolarization theory, (2) the repolarization theory and (3) the neural crest theory [11]. The depolarization theory is supported by mutations in the sodium channel leading to slow conduction and reentry. The repolarization theory is consistent with mutations related to the calcium or potassium genes causing a shortened action potential and phase 2 reentry. The neural crest theory relates to possibility of somatic mutations that result in local slow conduction [11].

Risk stratification and management

Numerous gaps in knowledge exist in optimal risk-stratification scheme for Brugada syndrome. Results of genetic testing currently don't influence prognosis or treatment [5]. Utility of electrophysiological study in establishing the diagnosis and risk stratification is still unclear [5]. Pharmacologic challenge with sodium channel blockers can expose latent electrocardiographic forms of the Bru-

gada syndrome. However, its sensitivity is reported to range from 15% to 100% [19,20].

Currently, there is no pharmacologic treatment preventing from VF occurring in patients suffering from Brugada syndrome. ICD implantation is the only effective treatment to reduce the risk of SCD [5]. According to ESC Guidelines ICD implantation is recommended in patients with diagnosis of Brugada syndrome and history of sudden cardiac arrest or who have documented spontaneous sustained ventricular tachycardia. Implantation also should be considered in cases of coexistence of spontaneous type 1 electrocardiographic pattern and syncope. ICD implantation may be considered in patients who develop VF during programmed ventricular stimulation with two or three extrastimuli at two sites. In patients with contraindication for an ICD and in patients who require treatment for supraventricular arrhythmias quinidine should be considered. Catheter ablation may be considered in patients with a history of electrical storms or repeated appropriate ICD shocks [5].

Management

The patient was qualified for immediate single chamber ICD implantation. He underwent the procedure without complications. The telemetric control showed correct cardiac device parameters, patient was discharged home in good general condition without symptoms. He didn't get recommendation for pharmacological treatment beyond oral potassium supplementation.

Qualification for ICD implantation was obvious since the patient had cardiac arrest due to VF mechanism, which is clear class IA recommendation for the secondary prevention of SCD [5]. The entirety of clinical course and results of conducted tests raised the question about the kind of final diagnosis. Diagnosis of this disease can often be very difficult and treacherous [21]. Being affected by the Brugada syndrome in this case seemed to have a fairly classic course with conventional onset risk factors (age, sex, cardiac arrest during rest [22]). Structural heart disease and other causes of sudden cardiac arrest were ruled out. Also there were no features of other primary arrhythmia syndrome.

However, a diagnostic type 1 Brugada ECG pattern wasn't exposed, and the result of performed sodium channel blocker challenge was unclear. According to 2015 ESC Guidelines [5] the criteria for Brugada Syndrome diagnosis (class I, level C recommendation) in this case were not met. On the other hand there are no clear guidelines for cases of patients with documented VF, Brugada type 2 ECG pattern and without either a spontaneous or drug-induced Brugada type 1 pattern. Taking into consideration that in the course of the disease electrocardiographic changes are transient or variable over time as well as reported variable sensitivity of pharmacologic challenge, despite raised doubts we decided to diagnose Brugada syndrome in this patient.

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