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Letter to the Editor

What can be done when asymptomatic patients discover they have Brugada syndrome? A case report of Brugada syndrome

Andrea Duarte Doetzer [a], Vanessa Santos Sotomaior [a], Marcos Henrique Bubna [c], Salmo Raskin [a,b,*]

[a] Center for Health and Biological Sciences at Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil
[b] Genetika, Laboratory and Center for Genetic Counseling, Curitiba, PR, Brazil
[c] Hospital Cardiológico Costantini-Curitiba, PR, Brazil

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ABSTRACT

Brugada syndrome is an inherited cardiac disorder associated with a specific electrocardiographic pattern, involving ST segment elevation in leads V1 to V3. When not spontaneously terminated, it can lead to ventricular fibrillation and sudden death. We present a case report of a young male whose brother suffered a sudden cardiac arrest while playing soccer. A novel mutation c.2678G>A was detected on the gene SCN5A through molecular diagnosis. The mutation was shown to be present in the individual, his daughter and his other brother. For patients with previous ventricular fibrillation and/or syncope, implantable cardiac device (ICD) is recommended. However, how can patients without symptoms but with a clear diagnosis prevent cardiac arrest?

To the Editor,

A 33-year-old male presented sudden death after 5 min of playing soccer. He regularly participated in sporting activities, however, three months prior to the event, he had manifested strong chest pain after climbing the stairs, possibly related to the cardiac disease. Brugada syndrome (BS) was the suspected cause. Subsequently his brothers (28 and 25 years old) and niece (9 years old) were submitted to clinical and genetic testing to discover if a mutation was present that could be related to this syndrome. Direct DNA sequencing was performed and all presented the same novel mutation at *SCN5A* gene's exon 16, chromosome 3p21 (Fig. 1). This mutation c.2678G>A results in a substitution Arg893His in the extracellular binding domain between the 5° and 6° segment of the second transmembrane domain of the protein codified by *SCN5A*, which is responsible for the alpha subunit of cardiac voltage-dependent channel pores.

Both brothers were tested with provocative electrocardiogram (ECG) and both presented a normal ECG pattern. One of the brothers, R.A., had presented atypical thorax pain, however, his echocardiogram and ergometric test were normal. The 24-hour Holter test presented 12 extra ventricular systoles. Another noteworthy outcome was the electrophysiological test, which showed a Brugada pattern type 2 in the beginning (Fig. 2-a) and altered to pattern 1 until the end of exam without any medication (Fig. 2-b). Additionally, three extra ventricular stimulations lead to ventricular fibrillation (Fig. 2-c and -d), defibrillated with 360J (Fig. 2-e).

The referred patient opted to implant the cardiac device (IDC) despite the absence of symptoms. Neither the two brothers nor the niece showed any symptoms until the last appointment.

Our results suggest an autosomal recessive inheritance of Brugada syndrome in this family. The parents as well as other members of the family did not present any symptoms that could be related to this disease. An alternative hypothesis would be autosomal dominant inheritance with reduced penetrance. A third possibility would be germinal mosaicism, for which neither parent has the mutation in somatic cells. In this case, the parents do not obligatorily present the mutation. Unfortunately, in the present case the parents did not agree to undergo genetic testing, to elucidate this matter.

How should asymptomatic family members be oriented in this type of situation? Sudden cardiac death is not predictable; however, some factors have been associated with a higher incidence of cardiac arrest.

First, a correct diagnosis of the BS is of great importance by means of an electrophysiological study (EPS). According to the guidelines of the European Society of Cardiology the EPS is recommended when there are symptoms or family history that could be related to the syndrome. There is a need for testing on different days due to variability of the ECG from several factors. Results may be modulated by large meal intake, autonomic imbalance, electrolyte imbalance, blood glucose, body temperature, and drug administration [1,2].

Asymptomatic patients with spontaneous ST segment elevation are considered at a higher risk of sudden death (cardiac arrest rate 14%) than those with ECG abnormality test induced by drugs (5%) [2].

* Corresponding author. Center for Health and Biological Sciences at Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil.
E-mail address: genetika@genetika.com.br (S. Raskin).

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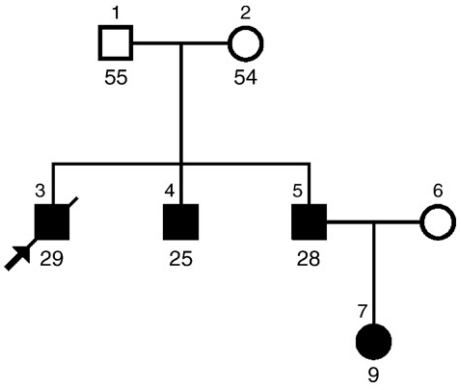

Fig. 1. Patient 3 is suspected to have Brugada syndrome. 4,5 and 7 have been diagnosed with a mutation on SCN5A gene and are assymptomatic. 1 and 2 are assymptomatic and were not tested.

There are no proven prognostic markers for asymptomatic patients, and therapeutic options should be individually evaluated. Febrile state was considered to be a cause of ventricular arrhythmia, as well as sports, alcohol, drugs, electrolyte disturbances, class I anti-arrhythmic medications, and other non cardiac medications and hormones [3].

Although the occurrence of polymorphic ventricular arrhythmias is predominant during rest or sleep, there are several cases of cardiac episodes in athletes during work-out or exercise. There are no conclusive studies regarding how the physical activity may trigger inactivation of the sodium channel, and until it can be elucidated, the practice should be carefully monitored.

Febrile state is a provoking factor for malignant arrhythmia. Furthermore, a local inflammatory process was associated with cardiac disturbance. The patients' general state of health while fever is present must be closely monitored, due to the possible induction of polymorphic tachycardia and ventricular fibrillation.

Implantable cardiac device (ICD) treatment is generally recommended for patients at higher risk of cardiac arrest, due to its cost as well as the inappropriate shocks that may occur. This treatment terminates ventricular arrhythmias, however, does not prevent future episodes. Only anti-arrhythmia drugs are indicated as a preventive treatment [4].

The role of these preventive drugs is to restore normal doming of the action potential, reducing the Ito current and increasing the calcium current. The first drug of choice would be quinidine, which prevents polymorphic ventricular tachycardia. Quinidine is a Class IA anti-arrhythmic drug that restores electrical homogeneity across ventricular myocardium and eliminates arrhythmia by phase 2 reentry. It is also recommended as adjunct therapy with ICD and can reduce the number of shock cases. Isoproterenol (adrenergic agent) increases calcium current and is the first choice for electrical storm suppression associated with BS. Cilostazol, sodalol and mexiletine have been successful in some cases. Tedisamil is an experimental brand cardiac agent that blocks the K+ repolarization of cardiac cells [2,4].

A cardio selective and Ito specific blocker would be an ideal drug; however, there are none commercially available.

There is a need of further studies regarding the prevalence of BS cases in the same family, the related symptoms, and risk stratification. A better understanding of how these prognostic markers may trigger cardiac arrest could define what to avoid for preventive management. Genetic tests are highly recommended, because the type of mutation may determine the severity of the phenotype. There have been published cases that lead to an autosomal dominant pattern inheritance, however, the family reported in this article may be either recessive or have reduced penetrance.

Subjects carrying a mutation that promotes the premature truncation of the protein are more prone to present syncope and develop a more severe phenotype than those with a missense mutation [5].

There are many studies in asymptomatic patients, but the treatments (either drug therapy or ICD implantation) have not been clearly defined as to which would have a better cost–benefit for these patients. Many patients opt for an ICD implant as a precaution of a cardiac event; however, considering the potential flaws of the device, we question whether or not these patients will have a better quality of life.

The analysis of the family data was approved by the Ethical Committee in Research at PUCPR, protocol 808/07.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [6].

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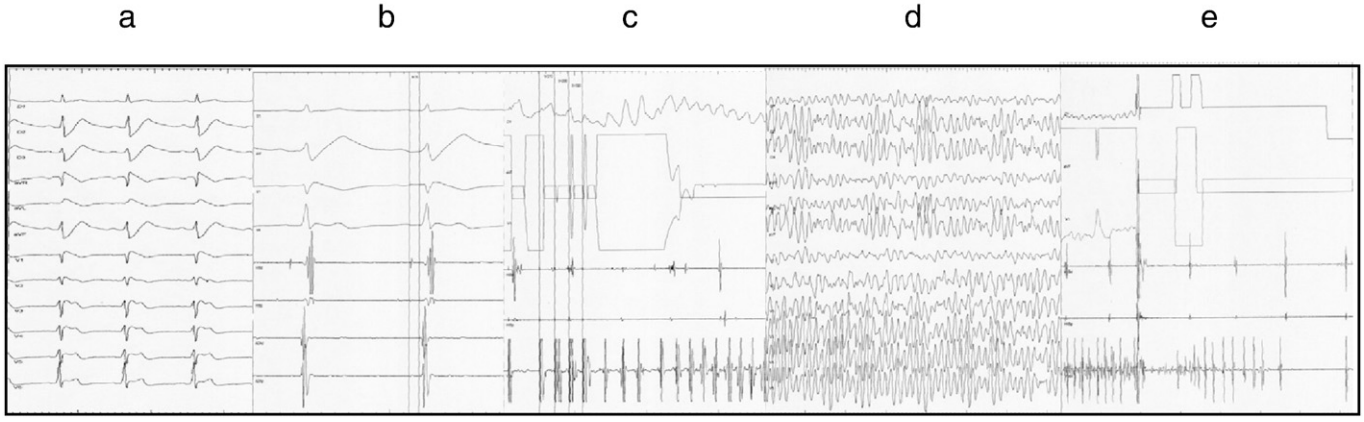

Fig. 2. R.A.'s electrophysiological test outcome. a- Basal ECG showing Brugada pattern type 2; b- Spontaneously turned into type 1 pattern of the syndrome and remained this pattern until the end of the exam; c- During ventricular stimulation it lead to ventricular fibrillation; d- Ventricular fibrillation; and e- Defibrillation with 360J.