Brugada syndrome: Identification of a new case

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ABSTRACT
Brugada syndrome is a primary electrical disorder in the absence of structural heart disease, associated with a significantly increased risk of sudden death in young individuals. Disputes increase after 25 years of its discovery, more than 300 mutations and several genes involved have been described. The case of a 44-year-old man with no personal or family history of cardiovascular disease, who manifests several syncopal episodes and whose baseline electrocardiogram shows a Brugada pattern. A pharmacological challenge test was performed and typical criteria to suggest the arrhythmogenic syndrome were detected. After the diagnosis, an automatic cardioverter-defibrillator was implanted attaining a favorable clinical course. Brugada syndrome can be diagnosed through surface electrocardiogram, which can prevent one of the leading causes of sudden cardiac death through the use of a defibrillator.

Key words: Brugada syndrome, Sudden death, Diagnosis, Implantable cardioverter-defibrillator

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RESUMEN
El síndrome de Brugada es un trastorno eléctrico primario, en ausencia de cardiopatía estructural, asociado a un significativo aumento del riesgo de muerte súbita en individuos jóvenes. A 25 años de su descubrimiento aumentan las controversias, se han descrito más de 300 mutaciones y varios genes involucrados. Se presenta el caso de un hombre de 44 años de edad, sin antecedentes personales o familiares de enfermedad cardiovascular, que manifiesta varios episodios sincopales y que en el electrocardiograma basal muestra un patrón tipo Brugada. Se realizó una prueba de provocación farmacológica que expresó típicamente los criterios para plantear el síndrome arritmogénico. Tras el diagnóstico se le implantó un cardioesfíbrilador automático con lo cual ha tenido una evolución clínica favorable. El síndrome de Brugada se puede diagnosticar a través del electrocardiograma de superficie, lo cual permite prevenir una de las principales causas de muerte súbita cardíaca a través del empleo de un cardioesfíbrilador.

Palabras clave: Síndrome de Brugada, Muerte súbita, Diagnóstico, Desfibrilador automático implantable
INTRODUCTION

The Brugada syndrome (BrS) was described as a disease in 1992 by Pedro and Josep Brugada. It is a primary electrical condition or cardiac channelopathy in a structurally healthy heart, genetically based, with autosomal dominant transmission and variable penetrance, whose diagnosis is based on the presence of characteristic changes of repolarization, located in the right precordial leads, and which entails risk of sudden cardiac death (SCD) secondary to polymorphic ventricular tachycardia, ventricular fibrillation or both.

From its description and until now, it has been studied in the main research laboratories worldwide, with the aim of finding a drug to control alterations resulting from genetic mutations. This would be a solution for one of the major causes of SCD in young patients, whose average age of presentation is between the third and fourth decades of life. This channelopathy affects five in 10,000 people in the world, although it is estimated that a large part of the population is undiagnosed due to asymptomatic forms of the disease. Geographically, it is much more common in Southeast Asian countries, where it represents the second cause of death in young people with a predominance in the male sex. In Cuba, the diagnosis is underestimated. Until 2003, 23 patients were assisted with this disease at the Instituto de Cardiología y Cirugía Cardiovascular of Havana; and in 12 of them, an implantable cardioverter-defibrillator (ICD) was implanted. The figure has been increasing steadily due to larger research on patients and families.

Given the dynamic nature of the electrocardiogram (ECG) and the ability of antiarrhythmic drugs of Class I to reproduce the typical electrocardiographic pattern, its administration has been used to expose the disease in individuals with normal or suggestive basal ECG, which does not meet the diagnosis criteria.

Taking into account the relatively short time of its discovery and the characteristics of the electrical signal, which may be intermittent, it is difficult to precise its exact incidence. In order to bring a new case, a patient diagnosed with Brugada is presented, corroborated with the application of the pharmacological challenge test, where the presence of syncope events was demonstrated and the patient was benefited, at the appropriate time, with the implant of an ICD.
CASE REPORT

History of the current illness
White male, 44 years old, with a health history and no family history of cardiovascular diseases, syncope or SCD, that in the last year had several events of sudden loss of consciousness, from which he recovered quickly with no residual neurologic manifestations. A surface 12-lead basal ECG was performed, and the patient was referred from the health area to the Department of Cardiology of the Provincial General Hospital from Sancti Spiritus, for possible ischemic heart disease. The ECG was repeated and the presence of a Brugada pattern was suspected, thus, a new ECG was performed with high position of the V1-V2 electrodes, where a very suggestive Brugada pattern type I was evident. It was decided to perform a pharmacological challenge test with flecainide 200 mg, and after 30 minutes it showed a type I pattern (coved type), more pronounced than in the spontaneous basal ECG. A transthoracic echocardiogram was also performed, where no evidence of structural heart disease was found.

No positive information was found from the complete physical examination. His heart rate (HR) was 93 beats per minute (bpm) and the blood pressure of 110/80 mmHg.

Complementary studies

Electrocardiograms
The first electrocardiogram, performed in the health area, showed: sinus rhythm, QRS axis 60°, HR 93 bpm, three-phase pattern of right bundle branch block with ST-segment elevation of 2 mm and negative T wave in V1-V2, without ST-segment depression in the opposite leads.

The second basal electrocardiogram, performed with high electrodes (Figure 1), showed–unlike the first one–, a QRS of 0°, HR of 74 bpm, and ST-segment elevation, with negative T waves in V1-V3, more clearly than in the previous ECG.

There were administered 200 mg of flecainide and 30 minutes later, another ECG (Figure 2A), was performed, which showed the presence of a QRS axis at -30°, similar HR, and a typical type I pattern of BrS, coved type. In the subsequent ECGs (Figure 2, B and C) the typical coved pattern remained more evident.

Figure 2. Electrocardiogram performed 30 (A), 45 (B), and 90 (C) minutes after the administration of flecainide, that showed a typical type I Brugada pattern (coved type).

Echocardiography
In the two-dimensional and M modes was confirmed the presence of cardiac chambers of normal size, preserved global and segmental cardiac contractility,
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Figure 3. Echocardiogram in two-dimensional and M modes (A), and mitral flowchart (B), which showed the presence of a structural and functional healthy heart.

competent valvular apparatus, no mass, no pericardial effusion, and inferior vena cava of 16 mm which collapses more than 50% in inspiration. The measurements were normal: interventricular septum 10 mm, posterior wall 9 mm, left ventricular diastolic diameter of 50 mm, systolic 33 mm, left ventricular ejection fraction of 63% and shortening fraction, 34% (Figure 3A).

The mitral diastolic flowchart showed a normal pattern, with a type I pulmonary flow curve, without pathological transvalvular gradients, and in the tissue Doppler imaging, no signs of ischemia were found in the three arterial territories (Figure 3B); therefore, the echocardiographic diagnosis was one of a structurally and functionally healthy heart.

Treatment
No pharmacological treatment was used and there was decided the use of an ICD that was implanted a month after the definitive diagnosis.

Follow-up and evolution
The patient, evaluated after the first month of the ICD’s implantation, remained asymptomatic, with no evidence of syncope, with proper functioning of the device, and without recorded arrhythmic events or inappropriate shocks of the ICD.

DISCUSSION
The BrS is cataloged, by several cardiology societies, within the group of channelopathies, secondary to an alteration of the ion channels' function of the cardiomyocytes in the absence of structural heart disease.

The familiar characteristics of the BrS are transmitted as an autosomal dominant with predominance (8:1) of the male sex; some authors suggest that it may have an esporadic pattern. Its high lethality has involved a significant boost to the genetic research in cardiology. Its electrocardiographic changes and clinical presentation are the most important issues, in addition to pharmacological challenge tests in individuals that are suspected to have the syndrome or in relatives of those that suffer it. In 1998, the first mutation was identified in the SCN5A gene, which encodes the alpha subunit of the cardiac sodium channel; then the GDP-1L was described, that seems to affect the transport of this channel to the cell surface and thus, until now, 80 mutations have been described in the same gene.

Currently, there have been identified mutations linked to the syndrome in over ten genes. Research in human hearts found significant differences in ion channels between the two sexes, which explains the higher frequency and worse evolution in the male one.

Despite the progress in the field of genetics, routine examinations in patients in whom the electrocardiogram is enough to confirm diagnosis are not recommended; but they do are in the first-degree relatives with high likelihood of having the genetic mutation that causes the syndrome.

Due to the recent recognition and still much research to do in this disease, it is difficult to give details of its incidence and distribution in the world. Published studies were analyzed, which suggest that
4-12% of unexpected deaths in young patients are due to this illness\textsuperscript{12}. Nademanedd \textit{et al.}\textsuperscript{13} recognize it as the most frequent cause of SCD below 50 years of age, in patients without previous cardiovascular disease. Naturally, when the incidence and prevalence of a disease is discussed, the physician observer cannot forget the importance of the attention and suspicion degree. In addition, there are easier types to diagnose and others less clear, as the ones intermittent and hidden\textsuperscript{12}. In other cases, the syndrome is not intended as probable diagnosis and there is a tendency to confuse it with other clinical situations as acute coronary syndromes, such as the patient presented in this report.

For its diagnosis, it is required the objectification of a characteristic pattern of repolarization, called type 1 or coved, in at least two right precordial leads (V\textsubscript{1}-V\textsubscript{3}), and less frequently in the inferior wall leads, characterized by prominent elevation of the ST-segment of convex morphology with amplitude of the J point > 2 mm, followed by negative T wave. Two other patterns of repolarization called type 2 and 3 of Brugada (Saddleback) are considered to be suggestive but not a diagnosis of the syndrome. Repolarization disorders, characteristic of the Brugada, have a dynamic nature. A patient may present the three electrocardiographic patterns at different times, as well as normal basal electrocardiograms\textsuperscript{1}.

There has been observed, with surface mapping, a greater ST-segment elevation in the area over the right ventricular outflow tract, with or without pharmacologic stress. The biggest changes are observed in V\textsubscript{2} at the normal level and high location of the electrodes\textsuperscript{14}.

The patient presented in this paper had several events of syncope at rest that, when interpreting the electrocardiogram in the health area, was wrongly diagnosed as ischemic heart disease; when testing with flecainide provocation, the typical pattern of the syndrome is more expressed. This coincides with the reviewed literature, where young patients with syncope and BrS suspicious electrocardiogram should be performed a pharmacological challenge test with sodium channels' blockers. There are other situations with electrocardiographic patterns that might be confused with this disease, as arrhythmogenic right ventricular dysplasia, aortic dissection, calcium disorders, pulmonary thromboembolism, myocarditis and coronary artery disease, especially acute myocardial infarction\textsuperscript{6}, as in the case presented. In these other diseases, the pharmacological test is never positive.

Since 1953, Osher and Wolff\textsuperscript{15} reported a dynamic electrocardiogram abnormality that simulated an infarction with no evidence of heart disease.

The ajmaline, flecainide or procainamide test, at therapeutic doses, modifies the electrocardiogram and allows a diagnosis by the appearance of the typical type 1 pattern. Only this pattern is considered a diagnosis of the disease, according to the agreement of 2005\textsuperscript{16}. Despite the superiority of ajmaline, it is not available in many countries and this has made flecainide to become the medication of choice in most electrophysiology laboratories\textsuperscript{17}.

Brugada \textit{et al.}\textsuperscript{18} showed, in their last series of 547 patients without previous cardiac arrest, that the presence of syncope increases by more than 2.5 times the probability of SCD or ventricular fibrillation after 2 years. With the same idea, Eckardt \textit{et al.}\textsuperscript{19} observed, in 212 patients, the occurrence of cardiac events in 6% of those who had suffered syncope and only 1% of the ones previously asymptomatic.

The case presented is consistent with the studies made so far regarding the time of appearance of symptoms. It is more often, evident and with worse prognosis in male patients, and higher risk of SCD in patients with type 1 pattern and syncope, with the inevitable indication of an ICD.

The only clearly proven treatment is the implantation of this device. The according consensus is that all symptomatic patients should receive this therapy\textsuperscript{20}, which would be classified as high risk of SCD by the presence of type I electrocardiogram and several syncope events.

The evolution of some patients with Brugada can be unpredictable, if they present syncope events, the behavior to follow is clear and there would not be necessary to perform programmed electrical stimulation studies; even if they were carried out, the result would be negative and the implantation of an ICD would persist, although the controversy still remains valid\textsuperscript{21}.

Given the enormous amount of valuable information gathered by many groups of researchers from the publication of the second agreement, there is necessary a review of the current diagnostic criteria, prognosis tools and treatment recommendations based, largely, on data emerging from exploratory trials\textsuperscript{22}.

**CONCLUSIONS**

This case illustrates the importance of thinking in the
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diagnosis of Brugada syndrome in young patients, without structural heart disease, but with syncope, for not confusing the electrocardiographic findings with other diagnosis and to be able to apply the pharmacological challenge test for the most obvious expression of the typical covered pattern and implanting an ICD, with the aim of preventing the SCD by malignant ventricular arrhythmias.

REFERENCES
