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A Typical, Relapsing Case of Brugada Syndrome

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Abstract

Brugada Syndrome (BrS) is a channelopathy classified as a primary electrical disorder that has been a subject of study in the past three decades because of its association with cases of Sudden Cardiac Death (SCD) in young, asymptomatic, and apparently healthy patients. The typical manifestations are syncope and cardiac arrest accompanied by characteristic electrocardiographic patterns. In the latest advances to understand this syndrome, it has been identified genes and multiple mutations that have allowed the elaboration of hypotheses related to repolarization and depolarization which aim to explain the physiopathological mechanisms. In this article, a case of a 32-year-old man with no history of cardiovascular disease who debuted with syncope and electrocardiographic changes in the right precordial leads suggestive of type II and type I Brugada pattern (after ajmaline test), is presented. Also, a review of the literature is carried out in terms of definition, classification, pathophysiology, genetics, prognosis and treatment for this entity.

Keywords: Brugada syndrome; Sudden cardiac death; Channelopathies; Ventricular fibrillation

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Abbreviations

BrS: Brugada Syndrome; SCD: Sudden Cardiac Death; RBBB: Right Bundle Branch Block; ECG: Electrocardiogram; ICD: Implantable cardioverter-defibrillator; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia; TTE: Transthoracic Echocardiogram; RVOT: Right Ventricular Outflow Rate; ICD: Implantable Cardioverter-Defibrillator

Introduction

BrS was first described in 1992 as a primarily electrical disturbance not associated with concomitant structural heart disease. The syndrome is characterized by ECG changes and can present with arrhythmias (usually premature ventricular complexes that can trigger VF or even monomorphic VT) or SCD. However, two-thirds of patients can be asymptomatic at the time of diagnosis [1,2].

Multiple causal mutations have been identified in different genes associated with sodium channels. Additionally, it has been observed that BrS predominantly affects middle-aged men. Therefore, timely diagnosis is of great importance due to the severity of the complications [1,2]. We present a young male patient with no significant cardiovascular history who exhibited the clinical manifestations and typical ECG abnormalities described in the literature.

Case Presentation

A 32-year-old man with no significant cardiovascular history presented to our institution with multiple recently developed symptoms including syncope, palpitations, asthenia, weakness, dyspnea on exertion, orthopnea, and chest pain radiating to the left arm, neck, and jaw. His personal history was unremarkable for any cardiovascular risk factors, but he did have a family history of interatrial communication, chronic kidney disease, diabetes, and hypertension.

The cardiovascular physical exam was normal. Previous electrocardiograms showed evidence of early repolarization in leads V1-V4, as well as an incomplete RBBB. In addition, the patient had a negative stress test for ischemia, which reported isolated extrasystoles during recovery. A TTE also did not show any structural alterations.

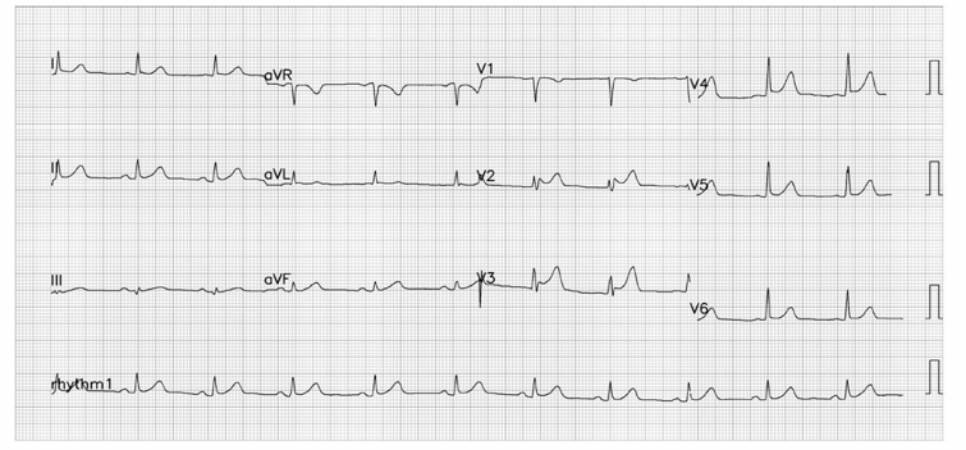

Figure 1: 12 derivations at rest ECG that shows J point elevation on V2-V3 with down-sloping of the ST-segment, compatible with type II Brugada pattern.

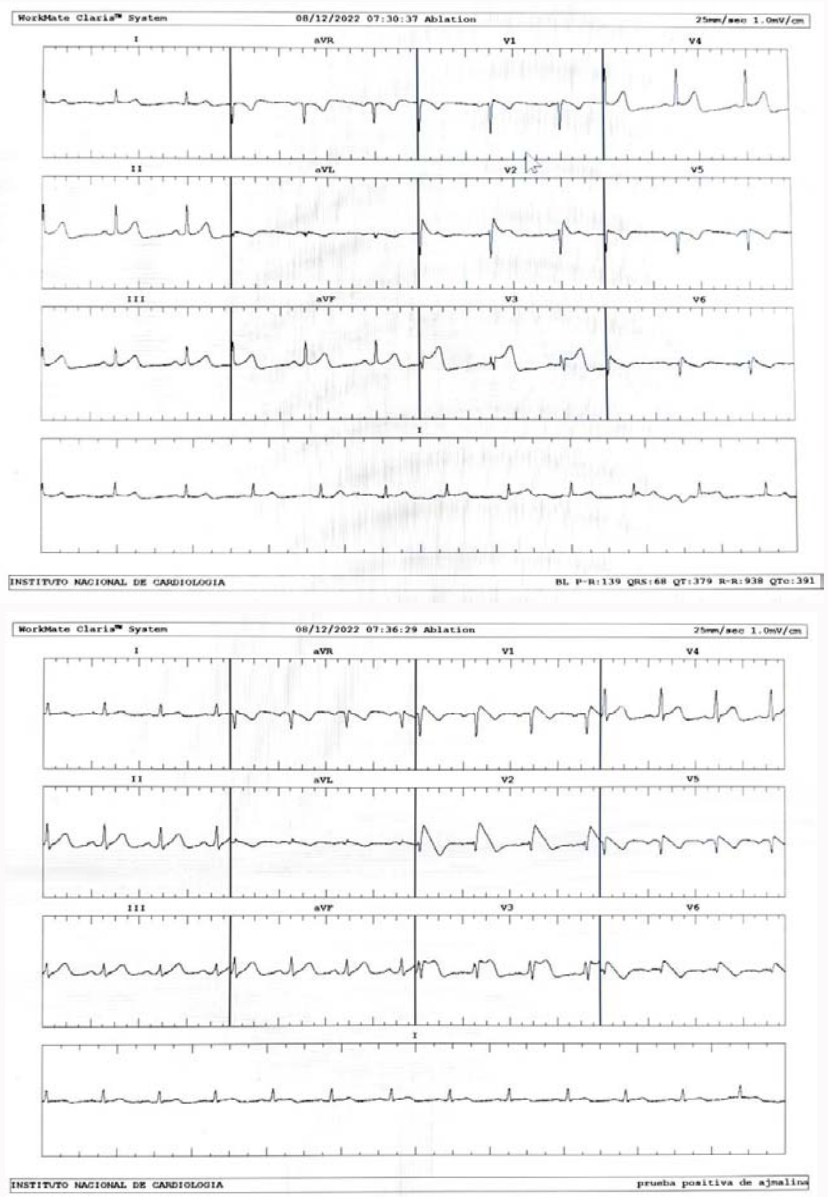

Figure 2: Ajmaline test that shows J point elevation greater than 2 mV with down-sloping of the ST-segment and continuity towards an inverted T wave, compatible with type I Brugada pattern.

An ECG was then performed, which revealed sinus rhythm, prolonged QT interval, and elevation of J point with a saddleback-shaped curve in the right precordial leads without T-wave inversion (Figure 1). Due to this finding, an Ajmaline test was performed (Figure 2), which showed J point elevation greater than 2mV with down-sloping of the ST-segment and continuity towards an inverted T wave, compatible with type I Brugada pattern.

Discussion

Definition and Epidemiology

BrS is an inherited disorder characterized by a pathognomonic abnormal ECG pattern that may be present spontaneously or unmasked by drugs as in the case exhibited. This syndrome increases the risk of serious arrhythmic events and SCD [1,3,4].

Researchers initially estimated that BrS was responsible for 4% to 12% [1], of cases of SCD in the general population, however, recent studies have suggested the prevalence is as low as 0.05% [3,5]. A review of global epidemiologic studies showed that the overall prevalence of BrS type I is ~1:2,000, while types II and III are around ~1:500 [1]. Males are approximately 2 to 9 times more affected than females [1,6].

BrS phenotypic expression appears to be age-dependent. The prevalence of BrS in children appears to be extremely low (~1:20,000) as it occurs mostly in adulthood, which is consistent with the highest incidence of SCD between 35 and 40 years of age [1,5]. BrS accounts for up to 28% to 50% of cases of SCD in apparently normal hearts [1,5].

Diagnosis

An expert consensus document was published in 2013, establishing two descriptive ECG abnormalities for BrS. Interestingly, the type III ECG pattern that was initially described is no longer considered within the classification [4,7].

Type I BrS is characterized by a "coved" ST-segment elevation, which is defined as J-point elevation with a gradual down-sloping of the ST-segment ≥ 2 mm, along with a negative T-wave in more than one right precordial lead (V1 to V3) [1,4]. Demonstration of type I BrS, either spontaneously or after a drug challenge, is considered a definitive diagnosis. Patients with BrS type II and III should undergo a sodium channel blocker-provoking test, as per guidelines [1,4].

Identification of the ECG pattern in one single lead- (V1 or V2) is enough to establish diagnosis, however, as more leads are affected, specificity grows. These ECG changes may present sporadically, fluctuate spontaneously or appear when under the influence of fever or medications [1,4,7].

Type II BrS or saddleback type (a new subtype that encompasses previous BrS patterns II and III) consists of a “saddleback” ST-segment with variable levels of elevation ≥ 0.5 mm (generally ≥ 2 mm in V2) in more than one right precordial lead, followed by a convex ST segment. The r′-wave may or may not overlap the J point, however, it has a slow downward slope. The ST segment is followed by a positive or biphasic T-wave in V2, with variable morphology in V1 [1,7].

Pathophysiology

The BrS has traditionally been considered a channelopathy in a structurally normal heart, with several debated electrophysiological theories attempting to explain the abnormal repolarization and depolarization phenomena. However, advancements in technology have allowed for the reconsideration of the disease's mechanism, suggesting a potential interplay between structural and functional changes in BrS [8]:

Repolarization hypothesis: A differential expression of transient outward potassium levels (Ito) between endocardium and epicardium which, when coupled with a reduced phase 0 inward sodium current (INa) due to sodium channel dysfunction which creates a transmural gradient across the myocardium causing the characteristic ST-segment elevation of BrS. This dispersion of repolarization between the layers is a proposed mechanism for ventricular arrhythmias in BrS [8].

Depolarization hypothesis: A reduced phase 0 INa causes conduction delay across the right ventricle, most marked in the RVOT, leading to the development of a gradient between the right ventricle and the delayed RVOT, causing initial ST elevation in the high precordial leads which overlie the RVOT. In later stages the gradient reverses back from the RVOT to the right ventricle accounting for T-wave inversion as current travels away from the high precordial leads [8].

Genetics

BrS is inherited in an autosomal dominant manner through chromosome 3 and the SCN5A gene, which encodes for the NaV1.5 channels associated with a type I pattern. However, only about 20% of patients with BrS have an identifiable SCN5A variant, which shows defective gating properties leading to conduction or repolarization abnormalities and the characteristic ECG patterns [1,3,9].

Furthermore, genes that code for the synthesis of potassium and calcium channels are also involved [1,5]. Other genes that have been implicated in BrS include SCN10A but the significance of these is disputed [1].

It is a genetically heterogeneous disease; therefore, the ECG manifestations are not identical, even when the responsible gene is the same, the exact mutation is different (at least 80 mutations have been associated with BrS) [1,3,9].

When a small percentage (<10%) of the fast sodium channels in the heart are affected, the ECG may not show any signs, and an Ajmaline test is required for diagnosis. If between 10 and 40% of the channels are affected, syncope caused by ventricular arrhythmias may occur, and SCD can be the first symptom. However, when more than 50% of the channels are affected, the condition is incompatible with life, leading to death in utero [9].

Prognosis

60% of patients present VF or cardiac arrest within the first year of diagnosis. 40% present SCD without adequate management [5,9].

Management

The management of BrS is mainly focused on preventing SCD and terminating any ventricular tachyarrhythmias through the use of an ICD [7]. Conservative measures are recommended for all patients with BrS, which includes avoiding drugs that can trigger Brugada ECG changes, managing fever with antipyretic treatment, limiting alcohol intake, and quickly addressing any metabolic disturbances. Asymptomatic patients with drug-induced BrS usually only require conservative measures [1].

Table 1: Candidates to receive ICD. ECG: Electrocardiogram; ICD: Implantable Cardioverter-Defibrillator; ^: Syncope; *: Requires close monitoring. Table extracted from: Asensio E, Álvarez B, Lozano E. Right bundle branch block, ST elevation, and sudden death: Brugada syndrome. Arch Inst Cardiol Mex. 2000;70:301-11.

Symptoms	ECG	History	Prolonged HV	Induction	ICD
Yes	Abnormal	Yes	Yes	Yes	Yes
Yes	Transient abnormality	Yes	Yes	Yes	Yes
No	Abnormal	Yes	Yes	Yes	Yes
No	Transient abnormality	No	No	Yes	Yes
Yes ^	Transient abnormality	No	No	No	No*

Currently available drugs which are effective in preventing arrhythmic episodes in BrS are quinidine, bepridil, and cilostazol or milrinone [3]. Quinidine and hydroquinidine have shown to be very effective in the management of BrS [1].

In patients with BrS who experience electrical storms, intravenous isoproterenol and phosphodiesterase III inhibitors are recommended where the mechanism is due to a VF [1].

The most effective treatment for BrS is an ICD which reduces mortality and cardiovascular mortality. However, complications such as lead failure and infections can occur [1,3,9]. Treatment should be personalized and closely monitored, based on specific criteria Table 1 [5,10]. Conservative measures can be sufficient for asymptomatic drug-induced BrS, and radiofrequency ablation can be considered as an adjunctive treatment in some cases [1,3].

Conclusion

The pathophysiological mechanisms of BrS are not fully understood yet, and even though many patients are asymptomatic, early diagnosis is essential to prevent serious complications. Identifying electrocardiographic patterns and taking a correct clinical history can guide a timely therapeutic approach.

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