JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 6, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.05.073

Long-Term Trends in Newly Diagnosed Brugada Syndrome

Implications for Risk Stratification

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ABSTRACT

BACKGROUND A proband of Brugada syndrome (BrS) is the first patient diagnosed in a family. There are no data regarding this specific, high-risk population.

OBJECTIVES This study sought to investigate the Brugada probands diagnosed from 1986 through the next 28 years.

METHODS We included 447 probands belonging to families with a diagnostic type 1 electrocardiogram Brugada pattern. The database was divided into 2 periods: the first period identified patients who were part of the initial cohort that became the consensus document on BrS in 2002 (early group); the second period reflected patients first diagnosed from 2003 to January 2014 (latter group).

RESULTS There were 165 probands in the early group and 282 in the latter group. Aborted sudden death as the first manifestation of the disease occurred in 12.1% of the early group versus 4.6% of the latter group ($p = 0.005$). Inducibility during programmed electrical stimulation was achieved in 34.4% and 19.2% of patients, respectively ($p < 0.001$). A spontaneous type 1 electrocardiogram pattern at diagnosis was present in 50.3% early versus 26.2% latter patients ($p = 0.0002$). Early group patients had a higher probability of a recurrent arrhythmia during follow-up (19%) than those of the latter group (5%) ($p = 0.007$). The clinical suspicion and use of a sodium-channel blocker to unmask BrS has allowed earlier diagnoses in many patients.

CONCLUSIONS Since being first described, the presentation of BrS has changed. There has been a decrease in aborted sudden cardiac death as the first manifestation of the disease among patients who were more recently diagnosed. These variations in initial presentation have important clinical consequences. In this setting, the value of inducibility to stratify individuals with BrS has changed. (J Am Coll Cardiol 2016;68:614–23)

Brugada syndrome (BrS) is an inherited cardiac arrhythmic disorder characterized by atypical electrocardiographic (ECG) patterns and an elevated risk of sudden cardiac death (SCD) (1,2). The disease is associated with mutations in the cardiac sodium channel gene *SCN5A* in 21% of patients (3,4). Patients with BrS can experience SCD due to rapid ventricular arrhythmias (generally polymorphic) and can endure other arrhythmias, such as atrial fibrillation (AF), atrial flutter, and other

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Manuscript received September 28, 2015; revised manuscript received April 17, 2016, accepted May 3, 2016.

supraventricular arrhythmias (1-7). Likewise, syncope can be the first and only manifestation of the disease. The disease is characterized by an ECG with a coved-type ST-segment elevation in the right precordial leads (V_1 to V_3) (1), but variations of this classic pattern have been described by our group (8).

Several clinical variables have been demonstrated to predict a worse outcome in patients with BrS. The occurrence of syncope, a spontaneous type 1 ECG, inducibility of ventricular arrhythmias during programmed electrical stimulation, and male sex have been shown in some studies to be related to the occurrence of cardiac events during follow-up (5-11), although debate regarding these predictors continues.

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No study has assessed in detail the characteristics of the first member (proband) diagnosed from each family with BrS. We sought to evaluate the change of their characteristics over time, and we hypothesized that the presentation of BrS has experienced an important change since the first consensus criteria.

METHODS

A "proband" was defined as the first patient diagnosed with BrS in a family on the basis of a type 1 Brugada ECG pattern. Since the first proband identified with BrS in 1986 by our group, all probands and family members have been prospectively included in a dual-center registry at the Free University of Brussels (UZ Brussel-VUB, Belgium) and at the University of Barcelona (Hospital Clinic, Spain) and followed in a prospective fashion. All patients included gave informed consent to participate in the registry. The ethics committee of the 2 centers approved the study protocol. For the purpose of this study, the database was assessed in January 2014.

A proband was included only if spontaneous or class I antiarrhythmic drug (ADD)-induced coved type I ≥ 2 mm ST-segment elevation in ≥1 lead from V1 to V3 was documented. A detailed family history was taken from each proband. Arrhythmic events, AF, and device implantation and complications related to this therapy during follow-up were recorded in the database.

The database was divided into 2 equivalent periods in accordance with the criteria for BrS in 2002 (2). The first period identified patients who were part of the initial study that became the consensus document on BrS in 2002 (early group). The second period reflected patients from 2003 until January 2014 (latter group).

The data recorded in the database were: 1) documentation of spontaneous or drug-induced ≥2-mm coved (type 1) Brugada ECG pattern; 2) personal and family history of aborted SCD (12); 3) history of syncope (at any age) or other symptoms; 4) sustained ventricular arrhythmia induced during the electrophysiological study (EPS); 5) arrhythmic event during follow-up and/or SCD; 6) implantable cardioverter-defibrillator (ICD) implantation and/or follow up; and 7) arrhythmic episodes, syncope, or appropriate or inappropriate shocks during the follow-up period.

The primary endpoint of the study was to identify the probability of first arrhythmic event at follow-up (defined as appropriate ICD shock for ventricular fibrillation or ventricular tachycardia or SCD) for the entire population of probands and for different subgroups.

DEFINITIONS AND TESTING. A type 1 Brugada ECG pattern was diagnosed if a coved-type ST-segment elevation of ≥2 mm followed by a negative T-wave was documented in >1 lead from V_1 to V_3 either spontaneously or after class I AAD administration (**Figure 1**) (2). If the ST-segment elevation was coved type, patients with negative/isoelectric or positive T waves were included and were classified as having a type 1 ECG pattern (7).

A class I AAD test was performed to unmask the diagnostic ECG pattern. Most frequently, 1 mg/kg of intravenous ajmaline administered within 5 min was used; less often, 2 mg/kg flecainide or 10 mg/kg procainamide given over a 10-min period were used for this purpose. The test was performed only in case of clinical suspicion of BrS: nocturnal agonal respiration, seizures, palpitations, pre-syncope, or chest discomfort, in addition to an ECG that was suggestive of BrS but does not fulfil the diagnostic criteria (e.g., type 2 Brugada syndrome). The test was considered positive only if a coved type 1 ECG was documented.

An EPS was performed only from the right ventricular apex and included 3 basic cycle lengths (600, 500, and 430 ms), with a minimum coupling interval limited to 200 ms and a maximum of 3 extra stimuli. The EPS result was only considered positive if a sustained ventricular arrhythmia (lasting ≥30 s, accompanied by syncope or requiring intervention for termination) was induced.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (interquartile range). Statistical differences were calculated using the chi-square test for discrete variables and the

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmia drug
AF = atrial fibrillation
ECG = electrocardiogram
EPS = electrophysiological study
ICD = implantable cardioverter-defibrillator
SCD = sudden cardiac death