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Drug-Induced Brugada Syndrome in Children

Clinical Features, Device-Based Management, and Long-Term Follow-Up

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Objectives The goal of this study was to investigate the clinical features, management, and long-term follow-up of children with drug-induced Brugada syndrome (BS).

Background Patients with BS <12 years of age with a spontaneous type I electrocardiogram have a higher risk of arrhythmic events. Data on drug-induced BS in patients <12 years of age are lacking.

Methods Among 505 patients with ajmaline-induced BS, subjects ≤12 years of age at the time of diagnosis were considered as children and eligible for this study.

Results Forty children (60% male; age 8 ± 2.8 years) were included. Twenty-four children (60%) had a family history of sudden death. Two (5%) had a previous episode of aborted sudden death, and 8 (20%) had syncope. Children experienced more frequent episodes of sinus node dysfunction (SND) compared with older subjects (7.5% vs. 1.5%; $p = 0.04$) and had a comparable incidence of atrial tachyarrhythmias. Children more frequently experienced episodes of ajmaline-induced sustained ventricular arrhythmias (VAs) compared with older patients (10.0% vs. 1.3%; $p = 0.005$). Twelve children (30%) received an implantable cardioverter-defibrillator (ICD). After a mean follow-up time of 83 ± 51 months, none of the children died suddenly. Spontaneous sustained VAs were documented in 1 child (2%). Among children with ICD, 1 (8%) experienced an appropriate shock, 4 (33%) had inappropriate ICD shocks, and 4 (33%) experienced device-related complications.

Conclusions Drug-induced BS is associated with atrial arrhythmias and SND. Children are at higher risk of ajmaline-induced VAs. The rate of device-related complications, leading to lead replacement or inappropriate shocks, is considerable and even higher than with appropriate interventions. Based on these findings, the optimal management of BS in childhood should remain individualized, taking into consideration the patient's clinical history and family's wishes. (J Am Coll Cardiol 2014;63:2272–9) © 2014 by the American College of Cardiology Foundation

Brugada syndrome (BS) is an inheritable syndrome characterized by coved-type ST-segment elevation in the right precordial leads (V_1 to V_3) and increased risk of sudden death (SD) in the absence of structural heart disease (1). Pharmacological challenge with ajmaline, a potent sodium channel blocker with a short half-life, is the recommended test to unmask the diagnostic Brugada electrocardiogram (ECG) pattern in patients with suspected BS and nondiagnostic ECG (2). Although in the initial description of a series of 8 patients with BS, 3 individuals were children (including the first and the second patients ever diagnosed with the syndrome), subsequent studies revealed that prevalence of BS in the pediatric population is extremely low (0.0098%) compared with the adult population (0.14% to 0.7%) (3,4). Moreover, the mean age of patients presenting with either symptomatic or asymptomatic BS is reportedly in the fourth or fifth decade (5). Clinical aspects and prognosis of either spontaneous or drug-induced BS have been previously described in individuals <16 years of age, and, as in adults, a higher risk of arrhythmic events has been found in symptomatic patients and in those displaying a spontaneous type I ECG (6). However, specific data on the clinical characteristics and prognosis of drug-induced BS in patients <12 years of age are lacking. In addition, no generally accepted or evidence-based guidelines are available for the specific therapeutic management of BS in this particular population and for the family screening of

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asymptomatic pediatric relatives of adult patients with BS and normal baseline ECG.

The purpose of the present study was to analyze our single-center experience of BS in children gathered over the last 20 years (since the first description of the syndrome). Particularly, our goal was to assess the clinical features, the based-device management, and the long-term follow-up of drug-induced BS in subjects ≤12 years of age at the time of diagnosis.

Methods

Study population. Since 1992, all consecutive patients diagnosed with BS by using an ajmaline challenge have been included in a registry and followed up in a prospective fashion. The ethics committee of the UZ Brussel-VUB approved the study protocol. A total of 505 patients with an ajmaline-induced diagnosis of BS were included in the registry from 1992 to 2013. In this group, 40 children were identified. Their data were used in the present study and compared with those of adult patients. Patients were considered as children if they were ≤12 years of age at the time of diagnosis (7). Physical examination, medical history, and baseline ECG were obtained, and underlying structural cardiac abnormalities were excluded in all patients. The recommendations of the Brugada consensus reports were used for establishing the diagnosis and for determination of candidacy for implantable cardioverter-defibrillator (ICD) therapy (8). Accordingly, ECGs were classified as Brugada coved-type (type I) or saddleback (type II) or normal. An ECG was considered diagnostic of BS if a coved-type ST-segment elevation ≥2 mm was documented in ≥1 lead from V_1 to V_3 in the presence or absence of a sodium channel blocker agent. Only patients with nondiagnostic baseline ECGs (normal ECG or Brugada type II ECG) were considered eligible for this study. All baseline and drug-induced 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV, with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space. All ECGs were analyzed by 2 independent experienced electrophysiologists; in case of disagreement, a third physician was consulted. Electrophysiological study (EPS) was performed at the investigators' preference in asymptomatic patients with BS to assess risk stratification. A maximum of 3 ventricular extrastimuli with a minimum coupling interval of 200 ms was delivered from 1 ventricular site unless ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) was induced.

Diagnosis of sinus node dysfunction (SND) was based on the correlation of symptoms with the presence of documented arrhythmias such as sinus bradycardia, sinus arrest, paroxysmal supraventricular tachycardia alternating with periods of bradycardia, or even asystole. Chronotropic incompetence, characterized by an impaired heart rate response to exercise, was considered as an additional manifestation of SND and was defined as failure to achieve 85% of the age-predicted maximum heart rate (9). Conventional 24- or 48-h Holter monitoring was performed in any case of suspected SND. Moreover, electrophysiological evaluation of SND was performed in all patients who underwent an EPS. Electrophysiological evaluation of SND included measurement of sinus node recovery time (SNRT), corrected SNRT (CSNRT = SNRT − sinus cycle length), SNRT/sinus cycle length × 100% (%SNRT), and sinoatrial conduction time estimated by using the method described by Narula et al. (10).

Abbreviations and Acronyms

AF = atrial fibrillation
AV = atrioventricular
BS = Brugada syndrome
ECG = electrocardiogram
EPS = electrophysiological study
ICD = implantable cardioverter-defibrillator
PVS = programmed ventricular stimulation
SD = sudden death
SND = sinus node dysfunction
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

Ajmaline challenge. Ajmaline (1 mg/kg) was administered intravenously over a 5-min period to unmask the diagnostic ECG pattern of BS in case of nondiagnostic basal ECG. Drug administration was usually performed under drug sedation by injection of a single bolus of propofol in patients <5 years of age. The test was considered positive for BS only if coved-type I ECG was documented in ≥1 right precordial lead (V_1 to V_3). Ajmaline infusion was discontinued before reaching the target dose if QRS prolongation exceeded 30% compared with the baseline interval, when frequent premature ventricular beats or type 1 Brugada ECG occurred, or in the case of development of high-degree AV block. All ECGs were analyzed before and after ajmaline administration. Heart rate, PR interval, QRS duration, and QTc interval (determined by using Bazett's formula) were measured in milliseconds. Maximal ST-segment elevation was measured at the J point in the right precordial leads (V_1 to V_3), and the analysis of ST-segment elevation was performed in lead V_1 and V_2 at 40 ms from the J point. ECG measurements were repeated after ajmaline challenge. Ajmaline-induced sustained ventricular arrhythmia (VA) was defined as the occurrence of VF or sustained VT (lasting at least 30 s, accompanied by syncope or requiring intervention for termination).

Genetic analysis. Genetic testing with sequence analysis of *SCN5A* was recommended for all children who had a diagnosis of BS. Genomic DNA was extracted from peripheral blood leukocytes by using standard protocols. If no mutation was identified, sequence analysis of other genes (e.g., *CACNA1C*, *SCN1B*, *KCNE3*, *SCN3B*) was considered. Mutation-specific genetic testing was recommended for family members and appropriate relatives, after identification of the BS-causative mutation in an index case. In this study, children having undergone genetic testing were only screened for mutation in the *SCN5A* gene.

ICD implantation. The decision to place epicardial versus endocardial ICD leads and the appropriate location for the