Impact of clinical and genetic findings on the management of young patients with Brugada syndrome

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BACKGROUND Brugada syndrome (BrS) is an arrhythmogenic disease associated with sudden cardiac death (SCD) that seldom manifests or is recognized in childhood.

OBJECTIVES The objectives of this study were to describe the clinical presentation of pediatric BrS to identify prognostic factors for risk stratification and to propose a data-based approach management.

METHODS We studied 106 patients younger than 19 years at diagnosis of BrS enrolled from 16 European hospitals.

RESULTS At diagnosis, BrS was spontaneous (n = 36, 34%) or drug-induced (n = 70, 66%). The mean age was 11.1 ± 5.7 years, and most patients were asymptomatic (family screening, (n = 67, 63%; incidental, n = 13, 12%), while 15 (14%) experienced syncope, 6(6%) aborted SCD or symptomatic ventricular tachycardia, and 5 (5%) other symptoms. During follow-up (median 54 months), 10 (9%) patients had life-threatening arrhythmias (LTA), including 3 (3%) deaths. Six (6%) experienced syncope and 4 (4%) supraventricular tachycardia. Fever triggered 27% of LTA events. An implantable cardioverter-defibrillator was implanted in 22 (21%), with major adverse events in 41%. Of the 11 (10%) patients treated with hydroquinidine, 8 remained asymptomatic. Genetic testing was performed in 75 (71%) patients, and SCN5A rare variants were identified in 58 (55%); 15 of 32 tested probands (47%) were genotype positive. Nine of 10 patients with LTA underwent genetic testing, and all were genotype positive, whereas the 17 SCN5A-negative patients remained asymptomatic. Spontaneous Brugada type 1 electrocardiographic (ECG) pattern (P = .005) and symptoms at diagnosis (P = .001) were predictors of LTA. Time to the first LTA event was shorter in patients with both symptoms at diagnosis and spontaneous Brugada type 1 ECG pattern (P = .006).

CONCLUSION Spontaneous Brugada type 1 ECG pattern and symptoms at diagnosis are predictors of LTA events in the young affected by BrS. The management of BrS should become age-specific, and prevention of SCD may involve genetic testing and aggressive use of antipyretics and quinidine, with risk-specific consideration for the implantable cardioverter-defibrillator.

KEYWORDS Brugada syndrome; Pediatrics; Arrhythmia; Quinidine; Genetics

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Introduction

Brugada syndrome (BrS) is an arrhythmogenic disease,[1] with a heterogeneous genetic background,[2–5] usually diagnosed during adulthood. Spontaneous Brugada type 1 electrocardiographic (ECG) pattern and symptoms are predictive risk factors for life-threatening arrhythmias (LTA) in adults,[2] but given the rarity of BrS in the pediatric population, risk stratification in the young is difficult.

In a Japanese study[6] screening elementary school children, only 0.02% of 22,000 displayed a Brugada type related ECG with only 1 case of spontaneous type 1 ECG pattern. The largest pediatric population with BrS studied so far included 30 European children and suggested that fever, symptoms, and spontaneous type 1 ECG pattern were associated with LTA.[7] Drug-induced BrS in children has been reported.[8] In the largest series of BrS in adulthood,[2] few patients were younger than 20 years.

Our objectives were to describe the clinical presentation of BrS below the age of 19, to identify prognostic factors useful to improve risk stratification, and to propose a data-based approach to management of this specific population.

Methods

Clinical data

Data on 106 patients younger than 19 years were collected from 16 European tertiary centers; 29 (27%) of them had been described originally in 2007.[7] Inclusion required a Brugada type 1 ECG pattern either spontaneously or after challenge with a sodium channel blocker (ajmaline or flecainide). Patients displaying only a fever-induced Brugada type 1 ECG pattern were included in the spontaneous group. The type 1 ECG pattern was defined according to consensus guidelines as coved-type ST-segment elevation $\geq$0.2 mV at its peak in at least 1 right precordial lead (leads V_1–V_3 in the second, third, or fourth intercostal spaces).[9,10]

Recorded data included family history; medical history; follow-up data from hospitalization reports, specialist, and general cardiology clinical letters; and direct follow-up contact with patients. Syncope was considered of arrhythmic origin when a sudden loss of consciousness occurs without any other explanation.

Twelve-lead ECGs at baseline and, if needed, during drug challenge were performed according to the guidelines.[10] Twelve-lead ECGs were first analyzed by an expert cardiologist in the referring hospital. ECG parameters were then collected at baseline and during drug challenge. Either intravenous ajmaline (1 mg/kg of body weight) or flecainide (2 mg/kg of body weight) was used depending on drug availability at the participating centers.

A baseline electrophysiology study (EPS) was performed in 22 (21%) patients at the clinical judgment of the expert cardiologist. A maximum of 3 ventricular extrastimuli with a minimum coupling interval of 200 ms were delivered from at least 1 right ventricular site unless ventricular fibrillation (VF) and/or sustained ventricular tachycardia (VT) were induced at an earlier stage.

At diagnosis, patients were considered symptomatic if they experienced aborted sudden cardiac death (aSCD), ventricular arrhythmias (nonsustained VT [NSVT], VT, or VF), or syncope. During follow-up, patients were considered to have an LTA event if sudden death or documented VT or VF occurred or if an appropriate implantable cardioverter-defibrillator (ICD) shock was documented.

Genetic analysis

Genetic testing was conducted according to the guidelines and was approved by local ethics committees for research or regular clinical purposes. Informed written consent was obtained from either the parents or the patient (if older than 18 years). Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All exons of *SCN5A* were amplified by the polymerase chain reaction. Polymerase chain reaction products were screened for an *SCN5A* mutation using denaturing high-performance liquid chromatography and/or direct DNA sequencing. In probands, all exons of *SCN5A* were screened whereas only the specific exon was sequenced if a rare variant had been identified previously in the family.

Statistical analysis

Data were analyzed with SAS packages (SAS Institute Inc., Cary, NC). The χ^2 or Fisher exact test was used to compare categorical variables. The *t*, Mann-Whitney, or Kruskal-Wallis test was use to compare continuous variables. ECG baseline data were corrected for age using the linear regression model. Data were presented as mean $\pm$ SD. Time data were presented as median (1st–3rd quartile). Time from diagnosis to the first event was analyzed using the Cox proportional hazards model. Hazard ratios (HRs), confidence intervals (CIs), and *P* values were calculated in univariate analysis. Log-rank *P* value was used if the Cox model was not relevant. Multivariate analysis was adjusted for variables with a *P* value of $<.15$ in univariate analysis using the Cox model. Survival curves were plotted using the Kaplan-Meier method. A *P* value of $<.05$ was considered statistically significant.

Results

Population

A total of 106 patients from 91 families were enrolled. The mean age at diagnosis was 11.1 $\pm$ 5.7 years, with a median (1st–3rd quartile) follow-up period of 54 (15–99) months, which was longer (117 [87–142] months; $P < .0001$) in the 29 children described in 2007.[7] Forty-six (43%) had a family history of SCD. Sixty-seven (63%) children were diagnosed below the age of 15, including 35 (33%) below the age of 8. Fifty-eight (55%) were male patients. No sex difference was observed below the age of 15 (sex ratio 1.03; 34 male and 33 female patients), but there was a trend toward male predominance above the age of 15 (sex ratio 1.60; 24 male and 15 female patients; $P = .32$).