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Characterization and Management of Arrhythmic Events in Young Patients With Brugada Syndrome

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ABSTRACT

BACKGROUND Information on young patients with Brugada syndrome (BrS) and arrhythmic events (AEs) is limited.

OBJECTIVES The purpose of this study was to describe their characteristics and management as well as risk factors for AE recurrence.

METHODS A total of 57 patients (age ≤20 years), all with BrS and AEs, were divided into pediatric (age ≤12 years; n = 26) and adolescents (age 13 to 20 years; n = 31).

RESULTS Patients' median age at time of first AE was 14 years, with a majority of males (74%), Caucasians (70%), and probands (79%) who presented as aborted cardiac arrest (84%). A significant proportion of patients (28%) exhibited fever-related AE. Family history of sudden cardiac death (SCD), prior syncope, spontaneous type 1 Brugada electrocardiogram (ECG), inducible ventricular fibrillation at electrophysiological study, and *SCN5A* mutations were present in 26%, 49%, 65%, 28%, and 58% of patients, respectively. The pediatric group differed from the adolescents, with a greater proportion of females, Caucasians, fever-related AEs, and spontaneous type-1 ECG. During follow-up, 68% of pediatric and 64% of adolescents had recurrent AE, with median time of 9.9 and 27.0 months, respectively. Approximately one-third of recurrent AEs occurred on quinidine therapy, and among the pediatric group, 60% of recurrent AEs were fever-related. Risk factors for recurrent AE included sinus node dysfunction, atrial arrhythmias, intraventricular conduction delay, or large S-wave on ECG lead I in the pediatric group and the presence of *SCN5A* mutation among adolescents.

CONCLUSIONS Young BrS patients with AE represent a very arrhythmogenic group. Current management after first arrhythmia episode is associated with high recurrence rate. Alternative therapies, besides defibrillator implantation, should be considered. (J Am Coll Cardiol 2019;73:1756–65) © 2019 by the American College of Cardiology Foundation.

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Brugada syndrome (BrS) is an inherited arrhythmic disease that may cause potentially fatal ventricular tachyarrhythmias, mainly in males between their fourth and fifth decade of life (1). Since the initial description of the disease in 1992, which involved 3 (37.5%) children (2), reports have mainly focused on adults who constitute the majority of symptomatic patients (3,4).

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Currently, the published data on children and adolescents with BrS and arrhythmic events (AEs) is limited. Among the largest published series of young patients with BrS comprising 30 to 128 patients, only very few patients (n = 1 to 10) presented as aborted cardiac arrest (ACA) or exhibited an AE during follow-up (n = 1 to 4) (5–10). Several risk factors for malignant ventricular tachyarrhythmias have been suggested in young BrS patients: a previous history of ACA or malignant syncope, spontaneous type 1 Brugada electrocardiogram (ECG), atrial arrhythmias, and conduction abnormalities (5–10). However, estimation of the utility of all proposed parameters for predicting the occurrence of AE in young BrS patients is hampered by the small symptomatic population size studied.

We recently reported the results of a multicenter international survey on AE in BrS (SABRUS [Survey on Arrhythmic Events in Brugada Syndrome]) in a large cohort of 678 BrS patients with their first ever documented AE, including a non-negligible number of young patients (1,11–13).

The purpose of the present paper was 3-fold: 1) to describe the clinical, ECG, electrophysiological, and genetic characteristics of a substantial cohort of young BrS patients (age ≤20 years) with documented AE; 2) to compare the characteristics of the pediatric (age ≤12 years) and adolescent age groups (age 13 to 20 years); and 3) to describe the management and follow-up of the young patients (age ≤20 years) after their first AE and assess possible predictors for AE recurrence.

METHODS

PATIENT SELECTION. Patients were included if they fulfilled the following 2 criteria: 1) presence of a spontaneous or drug-induced typical type 1 Brugada ECG; and 2) documented episode of first AE (sustained ventricular tachyarrhythmia).

As detailed elsewhere (1), a total of 678 BrS patients with first AE were recruited from 23 centers worldwide that agreed to collaborate in SABRUS. For the current project, all 23 centers were requested to provide additional baseline and follow-up data (see the following text) on all of their patients age ≤20 years who belonged to the original SABRUS cohort. Also, all centers were asked to provide data on any new young BrS patients (age ≤20 years) with an AE treated in their institution since the initial patient recruitment in April 2016. In addition, a new center was recruited following its published experience in young BrS

ABBREVIATIONS AND ACRONYMS

ACA = aborted cardiac arrest
AE = arrhythmic event
AFL = atrial flutter
AT = atrial tachycardia
BrS = Brugada syndrome
ECG = electrocardiogram
EPS = electrophysiological study
ICD = implantable cardioverter-defibrillator
SCD = sudden cardiac death
SND = sinus node dysfunction
VF = ventricular fibrillation
VT = ventricular tachycardia

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patients with AE (8-10). Overall, this enabled the collection of 57 young BrS patients with AE (including 10 new patients) who originated from a total of 24 centers. Of note, the current young cohort included some patients already previously reported (5-7,10).

The Institutional Review Board committees of all participating centers approved the study.

DATA ACQUISITION. As detailed elsewhere (1), the following data were collected for all study patients: 1) age at the time of the first AE; 2) mode of AE documentation (group A or B, see the following text); 3) sex; 4) proband status; 5) ethnicity (Caucasian, Asian, other, or unknown); 6) family history of sudden cardiac death (SCD); 7) prior history of syncope; 8) presence of spontaneous or drug-induced type 1 Brugada ECG (patients who exhibited spontaneous type 1 Brugada ECG changes even later after the index AE were counted as having spontaneous type 1 ECG); 9) whether or not the AE was associated with fever; 10) presence of *SCN5A* mutation; and 11) inducibility of sustained polymorphic ventricular tachycardia or ventricular fibrillation (VF) at electrophysiological study (EPS). Protocol of programmed ventricular stimulation was nonuniform among the various centers; however, it included at least 1 right ventricular site and ≤3 extra-stimuli.

The presence or absence of the following information was added: 1) sinus node dysfunction (SND) as defined elsewhere (9); 2) atrial arrhythmias; 3) first degree atrioventricular (AV) block (i.e., PR interval >200 ms); 4) intraventricular conduction delay, defined as QRS duration ≥110 ms; 5) QRS fragmentation, defined as ≥4 spikes in a single lead or ≥8 spikes in leads V_1, V_2, and V_3 (14); and 6) S-wave in ECG lead I (amplitude ≥0.1 mV or duration ≥40 ms) (15). Further collected data included whether a sodium channel blocker challenge test with ajmaline was performed and whether this was associated with ventricular arrhythmias (6,16). Information on patient management was also requested: 1) mode of management and follow-up after the first AE; and 2) clinical manifestation of the second AE if it occurred.

DEFINITIONS. Age groups. Young BrS patients were defined as age ≤20 years. This group of patients was further divided into a pediatric (age ≤12 years) and adolescent groups (age ≥13 and ≤20 years).

Patient presentation. The patients were classified into 2 groups according to the mode of AE documentation. Group A: Patients with documented ACA in whom the BrS diagnosis was made during work-up performed after ACA; Group B: Patients with a BrS diagnosis in whom prophylactic implantable cardioverter-defibrillator (ICD) implantation was performed for any reason and in whom an AE requiring appropriate ICD shock therapy was documented during follow-up by ICD interrogation.

Proband status. Proband was defined as the first patient of a family who has been diagnosed with the type 1 Brugada ECG (spontaneous or drug-induced). A nonproband was defined as a family member of a known BrS patient.

Genetic analysis. When an *SCN5A* mutation was identified, it was classified by its known pathogenicity, as previously reported (11).

STATISTICAL ANALYSIS. Differences in nominal variables between groups were assessed using a Pearson's chi-square test or a Fisher exact test as appropriate. Differences in continuous and ordinal variables between groups were assessed using a Mann-Whitney *U* test. Continuous and ordinal variables are shown as median (interquartile range) and nominal variables as n (%). Length of follow-up was evaluated using reverse censoring method. Univariate Cox regression was used to evaluate the association between each variable and AE recurrence. Kaplan-Meier curve was used to describe event recurrence during the follow-up time. The first AE was set as start of follow-up which continued until the recurrent AE or end of follow-up. The log-rank test was used to compare event recurrence between the 2 age groups and the potential risk factors.

Significant p values were considered when $p < 0.05$. All calculations were done using R version 3.3.2 from R Foundation for Statistical Computing (Vienna, Austria) or SPSS version 25 (IBM, Armonk, New York).

RESULTS

MAIN CHARACTERISTICS OF THE YOUNG BrS GROUP (AGE ≤20 YEARS) WITH AE. Table 1 displays the main characteristics of the young patient group. The cohort comprised 57 patients, median age of 14 years (interquartile range: 3 to 18 years) at time of first AE, most being males (n = 42; 73.7%), Caucasians (n = 40; 70.2%), probands (n = 45; 78.9%), and initially presenting with ACA (n = 48; 84.2%). The AE was fever-related in 28.1% of patients. A positive family history of SCD and a prior history of syncope were present in 26.3% and 49.1% of patients, respectively. A spontaneous type 1 Brugada ECG was observed in 64.9% of patients. Various conduction disturbances or atrial tachyarrhythmias were seen in 19.6% to 48% of patients. Most of the patients (56.1%) underwent an EPS during which VF was inducible in only 28.1%. Of note, only 1 patient from the pediatric group underwent a repeated test on quinidine and was still inducible.

Genetic testing was performed in 75.4% of patients, revealing an *SCN5A* mutation in 58.1%. AE during ajmaline test were present in 3 of 29 (10.3%) patients who were tested and included ventricular tachycardia (VT) followed by electromechanical dissociation (n = 1) and polymorphic VT (n = 1) in 2 pediatric patients and VT in 1 adolescent patient. Of note, the test was performed in 12 patients who also exhibited spontaneous type 1 ECG changes (see Online Appendix for details).

COMPARISON BETWEEN THE PEDIATRIC (AGE ≤12 YEARS) AND ADOLESCENT (AGE ≥13 AND ≤20 YEARS) GROUPS. The main comparative results are displayed in Table 1. A higher proportion of girls and Caucasians were noted in the pediatric group compared with the adolescent age group. In both groups (~84%), ACA was the initial manifestation of the disease. A detailed comparison between patients who presented with ACA (group A) or had their AE after ICD implantation (group B) is presented in Online Tables 1A to 1C. More AEs were associated with fever in the pediatric group. Pediatric patients were more likely to have spontaneous type 1 ECG, whereas other basic ECG features, SND, or atrial arrhythmias were equally distributed among the 2 groups. Atrial arrhythmias were seen in 9 pediatric patients including: atrial flutter (AFL) (n = 4), atrial fibrillation (n = 2), supraventricular tachycardia (SVT) (n = 1), atrial tachycardia (AT) (n = 1), and both SVT and AFL (n = 1). In the adolescent age group, atrial arrhythmias were seen in 8 patients: atrial fibrillation (n = 3), AFL (n = 1), SVT (n = 1), SVT and AFL (n = 1), AT (n = 1), and AT + AFL (n = 1). Other variables including proband status, presentation with an arrhythmic storm, family history of SCD, prior history of syncope, VF inducibility at EPS, occurrence of AE during Ajmaline test, and presence of a *SCN5A* mutation were not significantly different between the 2 groups.

MANAGEMENT AND FOLLOW-UP AFTER THE FIRST AE IN THE YOUNG GROUP. Follow-up and management data were available for 50 patients: 22 from the pediatric and 28 from the adolescent age group. Another 2 patients from the pediatric group deceased shortly after the first AE from neurological sequelae secondary to prolonged resuscitation. Table 2 summarizes patients' follow-up and management after their first AE.

Of the pediatric group, 15 (68.1%) had either arrhythmic death or recurrent ventricular tachyarrhythmia during follow-up, which was fever-related in 9 (60%). Besides the 2 patients described in the previous text, another 4 patients (18.1%) died during

TABLE 1 Comparison Between Pediatric (Age ≤12 Years) and Adolescent (Age ≥13 and ≤20 Years) Patients With Brugada Syndrome and an Arrhythmic Event

	Age ≤12 yrs (n = 26)	Age ≥13 and ≤20 yrs (n = 31)	p Value
Age at AE, yrs	3.0 (1.4–7.1)	18.0 (16.0–19.0)	<0.001
Sex			
Male	15 (57.7)	27 (87.1)	0.02
Female	11 (42.3)	4 (12.9)	
Ethnicity			
Caucasian	23 (88.5)	17 (54.8)	0.01
Asian	1 (3.8)	10 (32.3)	
Other/unknown	2 (7.7)	4 (12.9)	
Proband status			
Proband	19 (73.1)	26 (83.9)	0.44
Not proband	5 (19.2)	3 (9.7)	
Unknown	2 (7.7)	2 (6.5)	
Mode of AE documentation			
Group A	22 (84.6)	26 (83.9)	1.00
Group B	4 (15.4)	5 (16.1)	
Presence of fever during AE			
Yes	14 (53.8)	2 (6.5)	<0.001
No	12 (46.2)	25 (80.6)	
Unknown	0 (0.0)	4 (12.9)	
VF storm			
Yes	4 (15.4)	3 (9.7)	0.87
No	22 (84.6)	28 (90.3)	
Family history of SCD			
Yes	5 (19.2)	10 (32.3)	0.36
No	20 (76.9)	19 (61.3)	
Unknown	1 (3.8)	2 (6.5)	
History of syncope			
Yes	13 (50.0)	15 (48.4)	1.00
No	13 (50.0)	16 (51.6)	
Spontaneous type 1 BrS ECG			
Yes	21 (80.8)	16 (51.6)	0.03
No	5 (19.2)	15 (48.4)	
VF inducibility			
EPS performed	14 (53.8)	18 (58.1)	0.79
Inducible	3 (21.4)	6 (33.3)	0.69
Not inducible	11 (78.6)	12 (66.7)	
Presence of *SCN5A* mutation			
Testing done	24 (92.3)	19 (61.3)	0.02
SCN5A mutation	16 (66.7)	9 (47.4)	0.23
No *SCN5A* mutation	8 (33.3)	10 (52.6)	
Baseline ECG*			
First-degree AV block	9 (40.9)	10 (35.7)	0.77
IVCD (QRS >110)	11 (45.8)	14 (50.0)	0.79
QRS fragmentation	6 (28.6)	11 (40.7)	0.54
S in lead I	6 (30.0)	10 (35.7)	0.76
Other arrhythmias*			
Sinus node dysfunction	7 (30.4)	3 (10.7)	0.15
Atrial arrhythmias	9 (39.1)	8 (28.6)	0.55
Sodium channel blocker test*			
Performed	12 (50.0)	17 (63.0)	0.40
AE during test	2 (16.7)	1 (5.9)	0.55

Values are median (interquartile range) or n (%). *Data available for 24 children and 28 adolescents.

AE = arrhythmic event; AV = atrioventricular; BrS = Brugada syndrome; ECG = electrocardiogram; EPS = electrophysiological study; IVCD = intraventricular conduction delay; SCD = sudden cardiac death; VF = ventricular fibrillation.

TABLE 2 Patient Management and Follow-Up After the First AE

	Age ≤12 yrs (n = 22)	Age ≥13 and ≤20 yrs (n = 28)	p Value
Follow-up, months	39.00 (0.33–72.00)	71.00 (0.27–120.00)	0.14
Number of patients with second AE	15 (68.1)	18 (64.3)	0.23
Fever-related recurrent AE	9 (60.0)	1 (5.9)	0.002
Treatment, quinidine during part or all of follow-up	8 (36.3)	10 (35.7)	1.00
Clinical manifestation of second AE*			N/A
AE on quinidine	4 (26.7)	4 (22.2)	
VF storm on quinidine	1 (6.6)	1 (5.6)	
Death on quinidine	0 (0.0)	0 (0.0)	
AE without quinidine	6 (40.0)	12 (66.7)	
VF storm without quinidine	0 (0.0)	1 (5.6)	
Death without quinidine	4 (26.7)	0 (0.0)	

Values are median (range) or n (%). *The 2 patients from the pediatric group who died from neurological complications after the first AE are not included in the table.

FU = follow-up; N/A= not applicable; other abbreviations as in Table 1.

follow-up including 1 patient who died due to intractable ventricular tachyarrhythmia and 2 additional patients who exhibited post-discharge recurrent AE and SCD after 3.5 and 6.1 months, respectively, following their initial AE (ICD was not implanted in these patients). The last of these patients had a first AE at the age of 2 years, and a recurrence 9.9 months later; he died 16 years later from a VF storm despite wearing an ICD (17). None of the 6 patients mentioned were treated with quinidine. Another 11 patients had a recurrent second AE, including an arrhythmic storm in 1. These events occurred without antiarrhythmic therapy (n = 6) or while on quinidine therapy (n = 5, including 1 with VF storm). Of note, quinidine levels after the second AE were measured for 2 of these patients and were found below the therapeutic range in both cases.

Further analysis showed that of the 22 patients from the pediatric group with available follow-up, the first AE was fever-related in 12 (54.5%) and not fever-related in 10 (45.5%) (Online Table 2). Of the 12 patients with fever-related first AE, 7 of 8 (87.5%) recurrent AEs were fever-related. This contrasts with the finding that in the 10 patients whose first AE was not fever-related, only 2 of 7 (28.6%) recurrent AE was fever-related (p = 0.04).

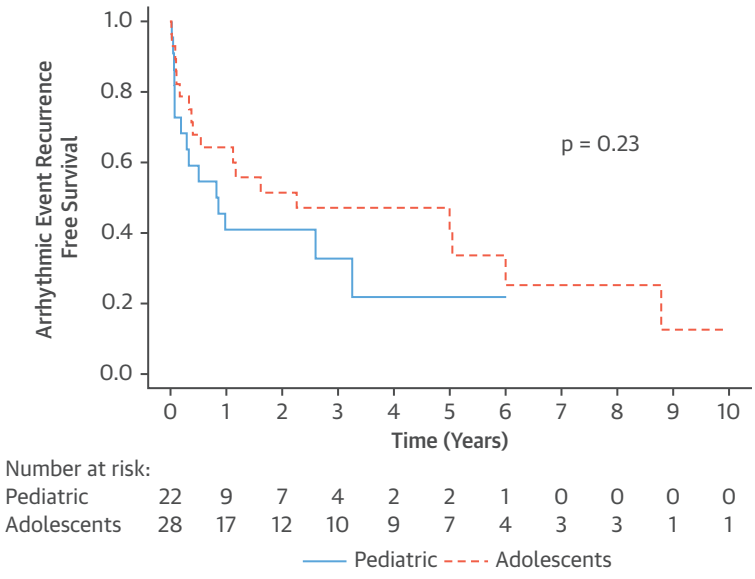
In the adolescent age group, no patient died during follow-up. However, 18 (64%) patients had a recurrent second AE: in 5 patients (including 1 with VF storm) it occurred during quinidine treatment, and in the remaining 13 (including 1 with VF storm) while not receiving antiarrhythmic therapy. In addition, of the 18 recurrent AEs, 15 patients had both first and recurrent AEs that were not fever-related and 1 patient with fever-related first AE had fever-related AE recurrence (p = 0.063). Of the 2 patients in whom the relationship to fever during the first AE was unknown, the recurrent AE was not fever-related in 1 and the relationship to fever during arrhythmia recurrence was unknown in the other.

The recurrent second AE was treated with endocardial right ventricular outflow tract ablation (n = 1) and epicardial ablation of the right ventricle (n = 4), all patients belonging to the adolescent age group. There were no AE recurrences following the ablation procedures in these 5 patients.

Kaplan-Meier curves describing time to recurrent AE in the pediatric and adolescent groups are presented in Figure 1. Both age groups demonstrated a similar high recurrence AE rate (p = 0.27) with median time to recurrence of 9.9 and 27.2 months, respectively. The 12-month recurrence AE rates were 59.1% and 35.7% for the pediatric and adolescent groups, respectively.

PREDICTORS OF AE RECURRENCE IN THE YOUNG BrS GROUP. The current analysis included 22 patients from the pediatric group and 28 patients from the adolescent group, of whom 15 and 18 patients had a recurrent AE, respectively. (Two patients from the pediatric group were excluded from the current analysis because, as stated in the previous text, they died shortly after the first AE from neurological sequelae secondary to prolonged resuscitation; therefore, whether they were at risk for recurrent AE cannot be determined.) Table 3 summarizes the variables that were significantly associated with AE recurrence. As shown, intraventricular conduction delay, the presence of S-wave in ECG lead 1, SND, and atrial arrhythmias were associated with recurrent AE in the pediatric group, while *SCN5A* mutation was associated with AE recurrence in the adolescent group (hazard ratio: 5.0; 95% confidence interval: 1.03 to 23.8; p = 0.045). Pediatric patients with 1 or more of the aforementioned risk factors had a hazard ratio: 6.9 (95% confidence interval: 1.9 to 25.2; p = 0.004) for recurrent AE compared with patients without any of these variables. The Central Illustration panel A shows Kaplan Meier curve for AE recurrence in pediatric patients with 1 or more risk factors compared with none. The median time for recurrent AE of pediatric patients with risk factors ≥1 was 2.3 months, while it was not reached in the subgroup of pediatric patients without any risk factor (p = 0.001). The Central Illustration panel B shows the Kaplan-Meier curve for AE recurrence in adolescent patients with or without *SCN5A* mutation. The median time for recurrent AE in *SCN5A* mutation carriers was 4.5 months, whereas it was 105.5 months in patients not carrying the *SCN5A* mutation (p = 0.03).

FIGURE 1 Kaplan-Meier Curve for Recurrent Arrhythmic Events Among Pediatric and Adolescent Patients



In both age groups, a high recurrence arrhythmic event rate (59.1% and 35.7% at 12 months, respectively; p = 0.27) was observed with median time to recurrence of 9.9 months and 27.2 months, respectively.

All other variables (Online Tables 2A and 2B), including sex, ethnicity, proband status, mode of AE documentation, fever-related AE, VF storm, family history of SCD, history of syncope, presentation with VF storm, spontaneous type 1 ECG, first-degree AV block, QRS fragmentation, and EPS results, were not associated with AE recurrence.

DISCUSSION

The current study includes the largest cohort of young BrS patients with an AE ever reported and illustrates 4 main findings: 1) marked differences between the characteristics of the pediatric and adolescent groups; 2) excessive AE recurrence rates among the pediatric and adolescent subgroups with short median time to recurrence; 3) fever-related first AE is associated with recurrence that is also fever-related, mainly in the pediatric group; and 4) several predictors for AE recurrence (i.e., more malignant disease) were defined for each of these 2 subgroups.

PREVIOUS STUDIES. Despite the enormous amount of publications on BrS since its first description (2), the number of BrS patients with AE reported in the published data is relatively small (1). Even more so in the young population, as attested in SABRUS, where the pediatric group (age <16 years) represented a minority of 4.3% (1). In 2007, Probst et al. (5) published the first largest pediatric series (age <16 years) that included 30 BrS children. In this cohort, 1 child presented with ACA and 3 others experienced SCD or appropriate ICD therapy during follow-up. Conte et al. (6) published a series of 40 children ≤12 years of age of whom 2 presented with ACA and 2 had AE during follow-up.

Lately, Gonzalez Corcia et al. (8-10) published several papers dealing with BrS in the young, in which the high age cutoffs for young age varied between age 19 and 25 years. Of the studied cohorts, up to 10 patients presented with aborted CA and up to 4 others had an AE during follow-up after diagnosis of BrS.

PEDIATRIC COMPARED WITH ADOLESCENT BrS PATIENTS. An advantage of the current study is the relatively high number of young patients included, which enabled the separate characterization of pediatric compared with adolescent patients. Among the main differences observed between these 2 groups was the higher proportion of girls in the pediatric group compared with the adolescent group. In addition, this study emphasized our previous observation that an Asian origin was rare among young patients (1), especially in the pediatric group. The study also confirms our previous report (12) on the predominant occurrence of fever-related AE in the pediatric

TABLE 3 Risk Factors for Recurrent AE

	Event Rate With Variable*	Event Rate Without Variable†	HR	95% CI	p Value
Age ≤12 yrs					
SND	7/7 (100)	7/14 (50)	3.3	1.1–9.7	0.03
Atrial arrhythmias	9/9 (100)	6/13 (46)	3.0	1.07–8.70	0.04
IVCD	9/9 (100)	6/13 (46)	3.4	1.2–9.8	0.02
Large S in ECG lead I	6/6 (100)	8/14 (57)	3.1	1.04–9.30	0.04
Either vs. none of the above	12/12 (100)	3/10 (30)	6.9	1.9–25.2	0.004
Age 13–20 yrs					
SCN5A mutation	8/9 (89)	3/8 (38)	5.0	1.03–23.80	0.045

*Number of patients with the variable and recurrent AE/total number of patients with the variable (%). †Number of patients without the variable and recurrent AE/total number of patients without the variable (%).

CI = confidence interval; HR = hazard ratio; IVCD = intraventricular conduction delay (QRS ≥110 ms); SND = sinus node dysfunction.

population. However, it shows for the first time that in the pediatric group, a substantial percentage (60%) of recurrences are also fever-related.

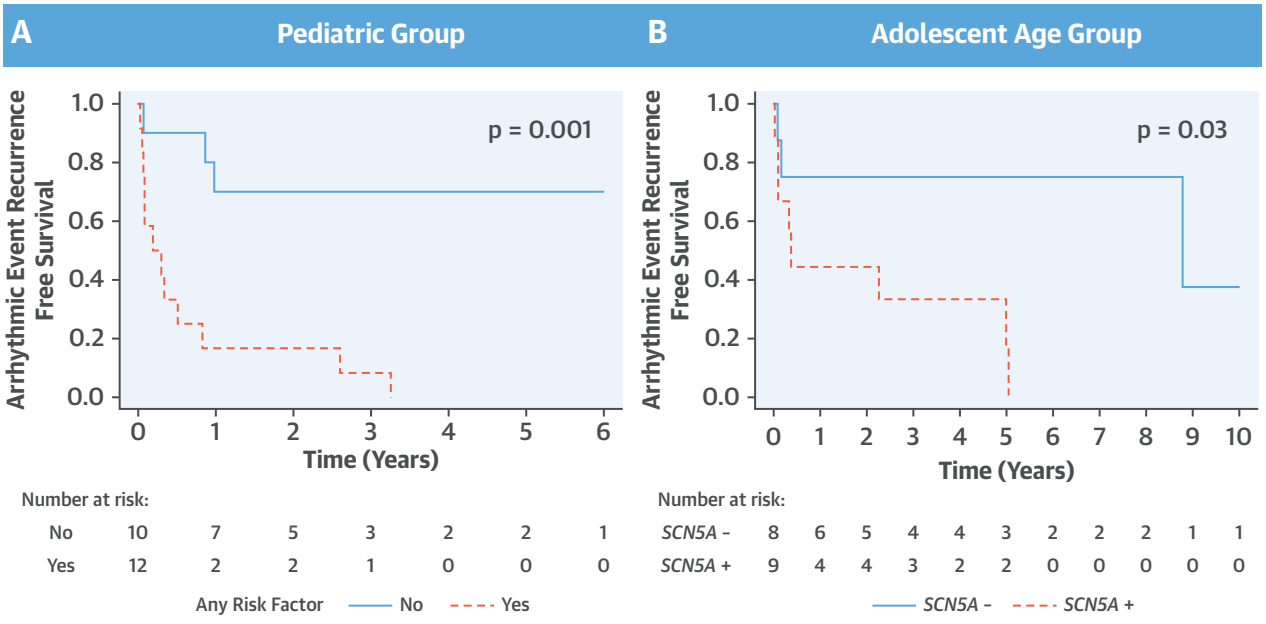
As in adults, spontaneous type 1 Brugada ECG is a known risk factor for AE in the young (5,7–9) and was observed in a substantial proportion (80.8%) of our pediatric patients with an AE. Of course, its absence cannot be entirely reassuring, as one-fifth of patients did not exhibit type 1 ECG. Interestingly type 1 ECG was not a predictive variable for AE recurrence (see the following text). A possible explanation could relate to the nature of our study, which exclusively included patients with an AE, thereby lessening the additional value of spontaneous type 1 ECG as a risk factor.

***SCN5A* MUTATIONS.** In the general population with BrS, *SCN5A* mutation rates vary between 14% and 26% (3,4,18–20). The present study found high mutation rates (58.1%) in the *SCN5A* gene of the young BrS patients with AE. However, conflicting results regarding the clinical significance of *SNC5A* mutations among young BrS patients have been reported. An earlier study by Andorin et al. (7) found *SCN5A* mutations in 77% of their 75 BrS patients age <19 years, and in all of their 9 patients (100%) who experienced an AE. Our group previously reported a much lower mutation rate (29.4%) in 201 asymptomatic BrS patients age <16 years (13). However, Gonzalez Corcia et al. (8) reported mutations rates of 45% (9 of 20) in symptomatic BrS patients (most with syncope) compared with mutation rates of 73% (24 of 33) in asymptomatic patients age ≤25 years. The latter could result from a bias related to screening of families with known *SCN5A* mutation causing artificial elevated number of asymptomatic patients with mutation. Overall, it seems that mutation rates among symptomatic young BrS patients are (much) higher than in symptomatic adults. One could question whether *SCN5A* mutations are associated with higher event rates in young BrS patients, which needs to be studied further. Still, it could also be argued that the high prevalence of *SCN5A* mutations in this cohort mirrors their earlier phenotype of BrS or severe conduction disease in an age category where a relevant arrhythmia trigger such as high fever is often occurring. In addition, the result of *SCN5A* mutations in these patients is often a use dependency (similar to flecainide intoxication). This will result in more severe conduction slowing at higher heart rates, which are common in children and even more so during fever or stressful episodes, resulting in a more pro-arrhythmogenic substrate. The only predictor of recurrent AEs in the adolescent population was indeed the presence of *SCN5A* mutation. Moreover, it is conceivable that in the patients in whom no genetic analysis was performed, there is a comparative prevalence of *SCN5A* mutations.

PATIENT MANAGEMENT. Several risk factors have been implicated as portending higher risk for AE in BrS. Undoubtedly, the most important risk factor is a previous AE (3,21,22). In various reports, the incidence of recurrent AE among ACA BrS survivors ranged from 40% to 70% at 10-year follow-up with a median time for recurrence >24 months (10,21,22). Gonzalez Corcia et al. (10) reported a 40% AE recurrence rate in a smaller cohort of 10 BrS patients age ≤20 years. In our cohort, we found similar AE recurrence rates of 68% and 64% in pediatric and adolescent patients, respectively. However, median time for AE recurrence was significantly shorter in patients exhibiting risk factors for recurrent AE, equaling 2.3 and 4.5 months in the pediatric and adolescent patients, respectively. The risk factors that were found predictive of AE recurrence include SND, intraventricular delay, atrial arrhythmias, and S-wave in ECG lead I in the pediatric population and *SCN5A* mutation among adolescents. Of note, the presence of S-wave in ECG lead I, which is a suggested risk factor for AEs in BrS (15), was not previously examined in the pediatric population. Thus, it seems that besides ICD implantation, urgent and prudent measures should be taken to prevent AE recurrence in patients exhibiting any of these risk factors. Gonzales Corcia et al. (10) reported 3 (8.5%) deaths due to VF storm in a cohort of young BrS patients wearing an ICD, which further strengthens the notion that ICD implantation without further treatment in high-risk patients may not be sufficient.

MEASURES TO PREVENT AE RECURRENCE. Despite apparently promising early results observed with

CENTRAL ILLUSTRATION **Arrhythmias in the Young With Brugada Syndrome**



Michowitz, Y. et al. J Am Coll Cardiol. 2019;73(14):1756–65.

(A) Kaplan-Meier curve for recurrent arrhythmic event (AE) among the pediatric patients with either none or 1 or more risk factor. Risk factors for recurrent AE in the pediatric group included: atrial arrhythmias, sinus node dysfunction, intraventricular conduction delay, or large S-wave in electrocardiogram lead I. Patients with risk factors had significantly higher AE rate that occurred earlier. **(B)** Kaplan-Meier curve for recurrent AE among the adolescents with or without *SCN5A* mutation. As shown, patients with positive mutation had significantly higher event rates that occurred earlier.

quinidine in the treatment of arrhythmic storms and the prevention of recurrent AEs in adults (23-26), the current study showed that approximately one-third of the recurrent arrhythmias in the young patients occurred during quinidine treatment without major difference between the pediatric and adolescent groups (**Table 3**). Nevertheless, any conclusion regarding the efficacy of quinidine in the young would be premature for the following reasons: 1) our study is observational and does not compare the prognosis of patients with or without quinidine; 2) doses of quinidine used could have been suboptimal; 3) problems related to patient compliance may be exacerbated in the pediatric age (27) (accordingly, quinidine levels were measured in only 2 young patients with an AE and were found below the therapeutic range in both); and 4) the efficacy of quinidine using EP-guided administration (26) previously found to show a high efficacy rate in adults has not been routinely practiced in any of the SABRUS centers in the young. Furthermore, the number of false-negative EP studies was very high in our cohort, further limiting its use. Thus, it seems that until confirmatory studies regarding quinidine efficacy and dosage in various age groups will be available, young patients on quinidine may be followed closely with repeat measurements of serum quinidine level. Also, the practice of EPS to test quinidine efficacy should be considered in case of inducible VF at baseline EPS. Another possible important therapeutic option is the use of beta-blockers to decrease the use of dependent phenotype in these young patients, as previously also suggested (28). Also, pro-active monitoring during (upcoming, e.g., vaccinations) fever, and antipyretic measures might be lifesaving. As many of the recurrent events were fever-related, especially in the pediatric group, it seems that fever is a medical emergency among pediatric BrS patients, especially those who experienced a previous fever-related AE. These children should be admitted immediately for observation and treatment in an intensive care unit. Whether combinations of quinidine and beta-blocker therapy are feasible and effective is currently insufficiently clear. Finally, it should be mentioned that all 5 adolescent patients from the current cohort who underwent ablation of their arrhythmias remained arrhythmia free during follow-up.

Although the numbers are too small to draw any significant conclusion, this option may be considered especially for young patients with recurrent AEs on quinidine or those who exhibit drug intolerance. de Asmundis et al. (29) recently reported the feasibility and efficacy of epicardial ablation at the time of abdominal ICD implantation in a 3-year-old child with BrS and recurrent quinidine refractory AEs. Such a case may inaugurate a novel therapeutic approach for children with severe ventricular arrhythmias. However, there is still insufficient data on the long-term sequelae of such ablation in very young patients.

STUDY LIMITATIONS. The current study is retrospective and observational in nature, and therefore, any conclusions regarding treatment efficacy or inefficacy should be taken with caution and further validated. Also, the number of Asian young BrS patients is limited especially in the pediatric group; thus, whether young Asians with BrS have a different risk profile than Caucasians should be further studied. Similarly, despite the study being the largest cohort of young BrS patients with an AE, the total number of patients is not enough to enable the performance of multivariate analysis to assess which variable is more significant than others in predicting AE recurrence. Yet, it should be emphasized that AE in young BrS patients is very rare. Finally, the current study, which is an extension of the SABRUS project, focused on young BrS patients presenting with an AE and there is no control group of patients without an AE.

CONCLUSIONS

The study presents a unique group of young (age ≤20 years) BrS patients with an AE. These patients display a specific unique baseline characteristic profile. Importantly, a sizeable number of these patients have an active and malignant BrS expressivity and measures other than ICD implantation seem mandatory to prevent harm from AE recurrence.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: BrS in young patients has malignant characteristics for which implantation of an automatic defibrillator may not be sufficient. In pediatric patients with a history of fever-related arrhythmic events, fever should be managed as a medical emergency, with such patients admitted to an intensive care unit and treated urgently with antipyretic measures.

TRANSLATIONAL OUTLOOK: Additional research is needed to define the optimum management of children and adolescents with BrS at risk or recurrent arrhythmias.

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KEY WORDS ablation, adolescence, Brugada syndrome, pediatric, quinidine, *SCN5A* mutation

APPENDIX For an expanded Methods section as well as supplemental tables, please see the online version of this paper.