

Clinical characteristics and risk of arrhythmic events in patients younger than 12 years diagnosed with Brugada syndrome

Daniela Righi, MD,^{*†} Luigina Porco, MD,^{*†} Camilla Calvieri, MD, PhD,^{*†} Pietro Paolo Tamborrino, MD,^{*†} Corrado Di Mambro, MD,^{*†} Simone Paglia, CCP,^{*†} Anwar Baban, MD, PhD,^{*†} Massimo Stefano Silveti, MD,^{*†} Maria Gnazzo, MD,[‡] Antonio Novelli, MD,[‡] Alberto Eugenio Tozzi, MD,[§] Fabrizio Drago, MD^{*†}

From the ^{*}Pediatric Cardiology and Cardiac Arrhythmias Unit, Department of Pediatric Cardiology and Cardiac Surgery, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [†]European Reference Network for Rare and Low Prevalence Complex Disease of the Heart (ERN GUARD-Heart), [‡]Medical Genetics Unit, Medical Genetics Laboratory, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, and [§]Multifactorial and Complex Diseases Research Area, Bambino Gesù Children's Hospital IRCCS, Rome, Italy.

BACKGROUND Brugada syndrome (BrS) is an inheritable disease with an increased risk of sudden cardiac death. Although several score systems have been proposed, the management of children with BrS has been inconsistently described.

OBJECTIVE The purpose of this study was to identify the characteristics, outcome, and risk factors associated with cardiovascular and arrhythmic events (AEs) in children younger than 12 years with BrS.

METHODS In this single-center case series, all children with spontaneous or drug/fever-induced type 1 Brugada electrocardiographic (ECG) pattern and younger than 12 years at the time of diagnosis were enrolled.

RESULTS Forty-three patients younger than 12 years at the time of diagnosis were included. The median follow-up was 3.97 years (interquartile range 2–12 years). In terms of first-degree atrioventricular block, premature beats, nonmalignant AEs, malignant AEs, and episodes of syncope, no significant differences were observed either between patients with spontaneous and drug/fever-induced type 1 Brugada ECG pattern or between female and male patients (except a significant difference between female and male patients for first-degree

atrioventricular block). A higher incidence of malignant AEs was observed in patients with syncope (3 of 8 [37.5%] vs 0 of 35 [0%]; $P = .005$) than in patients without syncope. *SCN5A* mutations were associated with a higher occurrence of malignant AEs (3 of 14 [21.4%] vs 0 of 25 [0%]; $P = .04$) compared with no *SCN5A* mutations.

CONCLUSION A spontaneous type 1 Brugada ECG pattern is not associated with a higher incidence of syncope, first-degree atrioventricular block, premature beats, nonmalignant AEs, and malignant AEs than the drug/fever-induced type 1 Brugada ECG pattern. Syncope events are correlated with an increased incidence of malignant AEs. Moreover, *SCN5A* mutations are associated with a higher occurrence of malignant AEs.

KEYWORDS Children; Brugada syndrome; Arrhythmic event; Type 1 Brugada ECG pattern; Syncope

(Heart Rhythm 2021; ■:1–7) © 2021 Heart Rhythm Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Brugada syndrome (BrS) is an inheritable syndrome characterized by coved-type ST-segment elevation in the right precordial leads (V_1 through V_3) and an increased risk of sudden cardiac death in the absence of structural heart disease.¹ BrS

may cause fatal arrhythmias, mainly in male patients between their fourth and fifth decades of life.²

Although the initial report included 3 children in a series of 8 patients with BrS,¹ subsequent studies revealed an extremely low prevalence of BrS in the pediatric population (0.0098%)³ compared with the adult population (0.14%–0.7%).⁴

In 2007, Probst et al⁵ reported their experience with the largest cohort of pediatric patients younger than 16 years with BrS. More recently, Michowitz et al⁶ provided additional data on BrS in patients younger than 12 years by enrolling children with BrS who had already experienced a

The authors have no funding sources to disclose. The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Fabrizio Drago, Pediatric Cardiology and Cardiac Arrhythmias Unit, Department of Pediatric Cardiology and Cardiac Surgery, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy. E-mail address: fabrizio.drago@opbg.net.

major arrhythmic event (AE), with the aim to identify the arrhythmic risk in this cohort of patients.

Several score systems have been proposed for risk stratification in pediatric patients with BrS.^{7,8} Unfortunately, the frequent lack of symptoms in this particular setting lowers the reliability of these scores.⁷

This study aims to identify characteristics, outcomes, and risk factors associated with cardiovascular events in children with a diagnosis of BrS younger than 12 years.

Methods

Study design and study population

This was a single clinical center case series. All patients referred to our tertiary care center between 2007 and 2018 with a diagnosis of BrS made at the age of <12 years were included in this retrospective observational study.

The diagnosis of BrS was confirmed according to the European Society of Cardiology guidelines.⁸ A spontaneous, fever-induced, or drug-induced type 1 Brugada electrocardiographic (ECG) pattern, recorded in the right precordial leads (V₁ through V₃) positioned in the second, third, or fourth intercostal space, was considered diagnostic. After diagnosis, no other ECG during fever was performed.

Patients who received a diagnosis of BrS as first in their family were defined as “proband.” Patients who were evaluated because of the positive BrS family history of their parents were defined as “family members.”

The study was approved by the institutional review board and fully complies with the Declaration of Helsinki as revised in 2013.

Patients' evaluation

At hospital admission, personal and family history of all patients was collected. Cardiac clinical evaluation was performed with M-mode and 2-dimensional Doppler echocardiography, standard 12-lead ECG, and 24-hour ECG Holter monitoring. The latter were performed in the right precordial leads (V₁ through V₃) positioned in the second, third, or fourth intercostal space, as recommended.⁷

Exercise testing on a treadmill was performed in all cooperative children (mainly younger than 6 years) according to the modified Bruce protocol using 3-minute stages with an incremental workload.

The head-up tilt test was performed in all cooperative children (usually younger than 8 years).

An electrophysiology study (EPS) was performed in our institute in patients with previous arrhythmias (high-risk patients). In some patients, EPS was performed in other centers before the admission to our institution.

An implantable loop recorder (ILR) was implanted when necessary.

Follow-up was scheduled every 6 months, and during each clinical evaluation, 12-lead ECG was performed by positioning leads V₁ and V₂ in the second, third, or fourth intercostal space.

We included in the study all events occurred in patients younger than 12 years. We also continued follow-up in all those patients who turned 12.

Data collection

Data collection included (1) age at the time of diagnosis, (2) presence of spontaneous or drug- and/or fever-induced type 1 Brugada ECG pattern, (3) proband status, (4) family history of sudden cardiac death, (5) sex, (6) genetic results, (7) symptoms (syncope and palpitations), (8) presence of atrioventricular (AV) or intraventricular conduction delay, (9) sinus node dysfunction (SND), (10) supraventricular and/or ventricular arrhythmias recorded by standard and dynamic ECG, (11) events during fever, (12) AEs recorded by cardiac device monitoring in patients with implantable cardioverter-defibrillator (ICD), pacemaker (PM), or ILR, and (13) EPS results.

The EPS result was considered positive when supraventricular and/or ventricular sustained or nonsustained supraventricular and/or ventricular arrhythmias were reproducibly inducible.

Event collected

The following events were analyzed during follow-up: (1) episodes of presyncope/syncope, (2) occurrence of first-degree AV conduction delay or block (PR interval > 160 ms), (3) occurrence of premature ventricular and supraventricular beats, (4) nonmalignant AEs (sustained supraventricular tachyarrhythmias, nonsustained ventricular tachycardias, and SND without symptomatic sinus arrest), (5) malignant AEs (sustained or polymorphic ventricular tachycardia [sVT], ventricular fibrillation, and symptomatic sinus arrest), (6) genetic testing results, and (7) invasive diagnostic or therapeutic procedure (EPS, ILR, PM, and ICD).

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes by our medical genetic laboratory. Genetic testing by clinical exome sequencing and targeted Sanger sequencing of *SCN5A* was performed. Informed consent for genetic analyses was obtained from parents/legal guardians.

Statistical analysis

Continuous variables were first tested for Gaussian distribution using the 1-sample Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean \pm SD and tested for differences using the Student unpaired *t* test. Non-normally distributed variables were expressed as median and interquartile range, and differences were tested using the Mann-Whitney *U* test. Categorical variables were expressed as percentages and analyzed using the χ^2 test or Fisher exact test, when appropriate.

All tests were 2-tailed, and analyses were performed using SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY).

Results

Study population

We enrolled 43 patients—34 probands (79%) and 9 family members (21%)—all from 43 different families.

The demographic and ECG characteristics of the study population are summarized in [Table 1](#).

Patients included were admitted for positive ECG screening (7 of 43 [16.3%]), positive BrS family history (7 of 43 [16.3%]), referral from other centers (22 of 43 [51.2%]), palpitations (1 of 43 [2.3%]), syncope after palpitations (1 of 43 [2.3%]), syncope during fever (1 of 43 [2.3%]), and supraventricular arrhythmias (4 of 43 [9.3%]).

Eight patients (18.6%) presented comorbidities ([Table 1](#)).

The median follow-up was 3.97 years (interquartile range 2–12 years), and no patient died during follow-up.

During the study, 15 of 43 patients (34.9%) turned 12.

We did not observe significant differences between male and female patients for mean age at the time of diagnosis (male patients 7 ± 2.7 years vs female patients 7.4 ± 2.5 years; $P = .68$) and for median years of follow-up (male patients 3.6 [interquartile range 3–5.7] vs female patients 3 [interquartile range 2–4.8]; $P = .356$).

During routine scheduled follow-up, of the 13 patients with spontaneous type 1 ECG pattern, 4 patients (31%) presented a constant pattern and 9 (69%) an intermittent pattern, whereas 4 of 30 patients (13%) enrolled with an induced type 1 ECG Brugada pattern presented an intermittent spontaneous type 1 ECG pattern ([Table 1](#)).

Table 1 Patients' clinical and demographic characteristics

Characteristic	Value	<i>P</i>
No. of patients	43	
Sex: M/F	25 (58)/18 (42)	.09
Age at diagnosis (y)	7.2 ± 2.60	
Race		
White	40 (93)	
Asian	1 (2.5)	
African	2 (5)	
Follow-up (y)	3.97 ± 3.07	
BrS ECG pattern		
Spontaneous	13 (30)	.0001
Drug- or fever-induced	30 (70)	
Fever-induced	24 (80)	
Drug-induced	3 (10) (PSVT treated with flecainide)	
	2 (6.7) (during propofol)	
	1 (3.3) (provocative test other center)	
Comorbidities	8 (18.6)	
Long QT syndroe	2 (4.6)	
Autism spectrum disorder	2 (4.6)	
Neurofibromatosis type 1	1 (2.4)	
Chromosomal abnormality	1 (2.4)	
Minor structural heart disease	2 (4.6) (ASD; small coronary artery fistula)	

Values are presented as mean \pm SD or n (%).

ASD = atrial septal defect; BrS = Brugada syndrome; ECG = electrocardiographic; F = female; M = male; PSVT = paroxysmal supraventricular tachycardia.

Event analysis

No significant differences in the occurrence of first-degree AV block, premature beats, nonmalignant AEs, malignant AEs, and episodes of syncope were observed between patients with spontaneous and induced type 1 Brugada ECG pattern ([Online Supplement](#)).

Moreover, no significant differences were observed between female and male patients in terms of syncope, premature beats, and malignant and nonmalignant AEs ([Table 2](#)).

Presyncope/syncope

Presyncope/syncope episodes were experienced by 8 patients (18.6%): 2 before BrS diagnosis and 6 during follow-up. The tilt test was used in 4 patients (50%) for differential diagnosis. Syncope was vasovagal in 4 patients because of arrhythmias in 2 (self-limiting sVT in one and 10-second sinus arrest in the other) and because of unknown causes in the remaining 2 (in 1, syncope occurred during fever).

AV conduction delay

Six patients (13.9%) showed first-degree AV block. The latter occurred in a patient before the admission to our center and during follow-up in the others. Moreover, it was more frequently observed in male patients than in female patients ([Table 2](#)) and was not related to a higher incidence of malignant AEs ($P = .99$).

Premature ventricular and supraventricular beats

Three patients (6.9%) had single premature beats (1 supraventricular and 2 ventricular). In the 2 patients with ventricular premature beats, a burden of $<1\%$ was recorded at ECG Holter monitoring. Patients with only premature beats did not experience malignant AEs.

Nonmalignant AEs

Eight patients (18.6%) developed nonmalignant AEs. An nsVT was recorded during Holter monitoring in 2 asymptomatic patients and during ILR monitoring in a symptomatic child. Asymptomatic atrial flutter (AF) was documented before BrS diagnosis in 2 patients (younger than 3 years). In one of these, AF was associated with SND and atrial septal defect (ASD).

An atrioventricular nodal reentry tachycardia was diagnosed in symptomatic child who showed a type 1 ECG Brugada pattern after oral flecainide therapy.

An ectopic atrial tachycardia was noted in 2 patients at the time of Holter ECG recording before BrS diagnosis.

All these nonmalignant AEs occurred within 12 years of age.

Malignant AEs

Three patients (6.9%) showed malignant AEs (an episode of sinus arrest during Holter monitoring; sVT induced by EPS and spontaneous during ICD monitoring; an episode of symptomatic sVT during follow-up and ventricular fibrillation during anesthesia induced by propofol). Patients

experienced all malignant AEs within 12 years of age and none during fever.

A significantly higher incidence of malignant AEs was observed in patients who experienced syncope than in those without syncope (3 of 8 [37.5%] vs 0 of 35 [0%]; $P = .005$). Instead, patients with nonmalignant AEs did not show a significantly higher incidence of malignant AEs (2 of 8 [33.3%] vs 1 of 35 [2.85%]; $P = .084$). Furthermore, all patients with malignant AEs were female (Table 2).

Genetics

Genetic testing was performed in 39 patients (90.7%); *SCN5A* mutations were documented in 14 of 39 patients (35.9%) (Table 3).

Data analysis highlighted a significant prevalence of malignant AEs in patients with *SCN5A* mutations compared with others (3 of 14 [21.4%] vs 0 of 25 [0%]; $P = .04$).

In contrast, no difference was observed between patients with and without *SCN5A* mutation in the occurrence of first-degree AV block (3 of 14 [21.4%] vs 2 of 25 [8%]; $P = .329$), premature beats (1 of 14 [7.14%] vs 2 of 25 [8%]; $P = .95$), nonmalignant AEs (3 of 14 [21.4%] vs 2 of 25 [8%]; $P = .329$), and episodes of syncope (3 of 14 [21.4%] vs 4 of 25 [16%]; $P = .686$).

Invasive procedures and device implantation

EPS was performed in 9 patients (20.9%) (Table 4), and the majority of patients had experienced episodes of arrhythmias before the study.

During follow-up, malignant and nonmalignant AEs were significantly more frequent in patients with positive EPS results than in those with negative EPS results (5 of 5 [100%] vs 0 of 4 [0%]; $P = .008$).

An ILR was implanted in 7 patients (16.2%): 4 (57%) symptomatic and 3 (43%) asymptomatic; in 3 of 4 symptomatic patients, the device was crucial to allow optimal decision making. No complications related to ILR implantation were observed during follow-up.

The characteristics of patients with ILR are summarized in Table 5.

Table 2 Sex-related incidence of symptoms, premature beats, and nonmalignant and malignant AEs

Symptom and event	Male patients (n = 25)	Female patients (n = 18)	P^*
First-degree AV block (n = 6)	6 (24)	0 (0)	.032
Premature beats (n = 3)	2 (8)	1 (5.5)	.999
Nonmalignant AEs (n = 8)	4 (16)	4 (22)	.7
Malignant AEs (n = 3)	0 (0)	3 (16.7)	.066
Syncope episodes (n = 8)	2 (8)	6 (33)	.052

AE = arrhythmic event; AV = atrioventricular.

*Analyzed using the Fisher exact test.

Table 3 Patients' genetic mutations

Patient no.	Mutation	Gene	Notes
1	Gly1408Arg	<i>SCN5A</i>	Heterozygous
2	Glu1784Lys	<i>SCN5A</i>	Heterozygous
3	Gln1518Ter	<i>SCN5A</i>	Heterozygous
4	Leu1786GlufsX2	<i>SCN5A</i>	Heterozygous
5	Arg219Cys	<i>SCN5A</i>	Homozygous
6	Arg179Ter	<i>SCN5A</i>	Heterozygous
7	Arg179Ter	<i>SCN5A</i>	Heterozygous
8	Ser1458Phe	<i>SCN5A</i>	Heterozygous
9	Arg814Gln	<i>SCN5A</i>	Heterozygous
10	Arg1583His	<i>SCN5A</i>	Heterozygous
11	Pro1506Thr	<i>SCN5A</i>	Heterozygous
12	Ala572Phe	<i>SCN5A</i>	heterozygous
13	Gln1033Arg	<i>SCN5A</i>	Heterozygous
14	Thr143Ala	<i>SCN5A</i>	Heterozygous

Four patients (9.3%) underwent device implantation (PM in 1 [2.3%] and ICD in 3 [6.9%]).

A 2-year-old boy with ASD underwent EPS because of SND and episodes of AF. AF was inducible at the time of EPS and sedation with propofol unmasked a type 1 Brugada ECG pattern. Thus, this patient underwent epicardial DDD PM implantation, surgical closure of ASD, and surgical radiofrequency ablation of the cavotricuspid isthmus. However, the child experienced recurrent AF and new episodes of atrioventricular nodal re-entry tachycardia. Thus, hydroquinidine and propranolol were successfully administered.

No complications related to PM implantation were observed during follow-up.

A 2-year-old girl underwent EPS for AF and syncope-associated sVT. Sedation with propofol unmasked a type 1 Brugada ECG pattern with spontaneous occurrence of ventricular fibrillation that was interrupted with direct current shock. An epicardial ICD was implanted, and hydroquinidine (6 mg/kg) and nadolol (0.5 mg/kg) were successfully administered.

A 10-year-old girl with BrS and long QT phenotype showed nonsustained ventricular tachycardia recorded at ILR monitoring during an episode of presyncope. She underwent EPS, and a reproducible induction of sVT was observed; hence, a transvenous ICD was implanted and nadolol (0.5 mg/kg) was administered. No malignant AEs occurred during follow-up. Hydroquinidine was not administered to this patient because of the *SCN5A* genetic mutation (Glu1784Lys) that was associated with a double ECG phenotype (BrS pattern and long QT). In this patient, the QT value was always lower than 500 ms and no arrhythmias were documented during 7.5-year follow-up.

A 7-year-old boy with spontaneous BrS pattern and syncope during fever underwent epicardial ICD implantation with a subcutaneous coil. No episodes of arrhythmias were recorded during 12-year follow-up.

During a median follow-up of 3.97 years (interquartile range 2–12 years), complications occurred in all ICD-implanted patients: inappropriate shock due to AF (in the

Table 4 Results of EPS

Patient no.	EPS indication	Inducibility	ICD	ILR	Follow-up
1	nsVT at Holter ECG	No arrhythmias	—	—	No arrhythmias
2	nsVT at ILR	sVT	+	+	1 sVT (30 s) at ICD
3	AF and sVT	VF	+	—	AF
4	Performed in another center	—	—	—	No arrhythmias
5	SVT (ectopic) at Holter ECG	SVT (ectopic)	—	—	Performed RFCA No arrhythmias
6	nsVT	nsVT	—	+	5 Asymptomatic nsVT at ILR
7	Palpitations	—	—	+	No arrhythmias Symptoms
8	AF	AF	—	—	PM implantation/AF nodal reentry tachycardia on therapy
9	Performed in another center	—	—	+	No arrhythmias No symptoms

AF = atrial flutter; ECG = electrocardiography; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; nsVT = nonsustained ventricular tachycardia; PM = pacemaker; RFCA = radiofrequency catheter ablation; SVT = supraventricular tachycardia; sVT = sustained ventricular tachycardia; VF = ventricular fibrillation.

patient with epicardial ICD), inappropriate shock due to noise oversensing requiring transvenous ICD lead extraction and reimplantation, and subcutaneous coil migration due to growth requiring coil reimplantation.

Discussion

The outcome and management of patients younger than 12 years with BrS are inconsistently described in the literature.^{3,6,9} Only Conte et al³ reported the clinical features of a pediatric population younger than 12 years, but patients with a spontaneous Brugada ECG pattern were excluded. More recently, Michowitz et al⁶ compared the outcome of patients younger than 12 years with BrS with that of adolescents (13–20 years), but only patients who had already experienced an AE were included.

As far as we know, this is the first study describing the outcome and management of children younger than 12 years with spontaneous or drug/fever-induced type 1 Brugada ECG pattern without previous episodes of arrhythmias and including a very high proportion (79%) of probands.

Overall, our single-center study provides 2 main contributions to the literature. First, it includes a large study sample, which is due to the possibility to enroll a very high number of patients coming from general ECG screening and from other institutions. Second, this study includes a significantly high proportion of children with drug/fever-induced Brugada ECG pattern given that spontaneous type 1 Brugada ECG

pattern can be found in only very few children.⁹ The latter finding could be related to age and hormonal differences.¹⁰ However, in our population this relation could be excluded considering that the mean age of patients with spontaneous BrS ECG pattern (7.19 years) did not differ from that of patients with fever- or drug-induced Brugada ECG pattern (7.20 years) and that no sex predominance was observed in the whole patient cohort.

Some literature data on patients with BrS younger than 19 years reported that spontaneous type 1 Brugada ECG pattern and symptoms should be considered as major predictors of severe AEs.^{5,11,12} Differently, our group describe a spontaneous type 1 Brugada ECG pattern that does not seem to be associated with a higher risk of malignant or nonmalignant AEs, according to results reported by Michowitz et al.⁶ Moreover, the lack of correlation between spontaneous type 1 Brugada ECG pattern and a higher risk of AEs could be explained by the variability of the ECG pattern, which seems to uphold the variability of the Brugada ECG pattern over time as reported by Richter et al.¹³

Our study shows an increased incidence of malignant AEs in patients younger than 12 years with syncope. Interestingly, 1 of 3 patients with malignant AEs (sVT and syncope) had a positive head-up tilt test result but also an inducible VT at EPS. Actually, patients with BrS seem to show a higher level of parasympathetic activation and a smaller level of sympathetic activation compared with control subjects, supporting the possible coexistence of various types of syncope events

Table 5 Characteristics of patients with ILR

Patients with ILR	Indication for implantation	Symptoms during monitoring	ECG findings
Asymptomatic (n = 3)	Positive family history	No symptoms	No arrhythmias
Symptomatic (n = 4)	1 Palpitation	Palpitations	No arrhythmias
	1 Syncope and palpitation	Palpitations	5 Episodes of nsVT
	1 Sinus arrest during Holter monitoring	No symptoms	No other arrhythmias
	1 Presyncope in BrS and long QT syndrome	Palpitations	nsVT

BrS = Brugada syndrome; ECG = electrocardiographic; ILR = implantable loop recorder; nsVT = nonsustained ventricular tachycardia.

experienced by these patients.¹⁴ All these findings, in accordance with the data recently reported in patients younger than 19 years,¹¹ suggest that careful evaluation should be performed in very young patients with BrS and episodes of syncope,⁷ even in the case of apparently obvious vasovagal characteristics of the event, and that >1 type of syncope could coexist in a patient with a diagnosis of BrS.

Recently, Andorin et al¹¹ reported that in young patients with BrS, differently from adult patients with BrS,² sex differences do not represent a risk factor for malignant AEs. In the present study, we observed a higher frequency of malignant AEs and episodes of syncope in female patients, although statistics were not significant, possibly because of the small sample size ($P = .066$ and $P = .052$, respectively). Indeed, a significantly higher incidence in young female patients was previously reported in the Survey on Arrhythmic Events in Brugada Syndrome² and it could suggest that the reduction of the propensity for arrhythmias¹⁵ in postpubertal female patients with BrS vs male patients could be due to female hormones, which decrease the expression of I_{to} (transient K potassium current) channels in the right ventricular epicardium. However, further studies with larger cohorts of patients are needed to confirm these data.

In the general population with BrS, *SCN5A* mutation can be observed in the 14%–26% of cases.^{16,17} In this study, a *SCN5A* mutation was found in 14 (35.9%) whereas no gene mutations were identified in the remaining 25 patients (64.1%). These data differ slightly from those of Gonzalez Corcia et al,¹² who reported genetic mutations in 27% of patients with BrS younger than 13 years, and those of Michowitz et al,⁶ who reported a higher prevalence (66%) of *SCN5A* mutations in patients younger than 12 years. Nevertheless, our data seem to be more consistent considering the high number of patients who underwent genetic testing (93%), the absence of brothers or sisters in the selected cohort, and the high percentage of probands (79%).

The clinical significance of *SCN5A* mutations in young patients with BrS is still a matter of debate. The majority of data available in the literature^{11,12,18} do not recognize a role to genetic mutations in risk stratification. Only Michowitz et al⁶ reported an increased risk of recurrent AEs in adolescent patients with BrS carrying *SCN5A* mutations, but not in those younger than 12 years. On the contrary, our study clearly shows, for the first time, a significant association between *SCN5A* mutations and the occurrence of malignant AEs in children younger than 12 years. However, further studies with larger cohorts of patients are needed to confirm this important finding.

In the 2015 European Society of Cardiology guidelines,⁸ no clear definition of the prognostic value of EPS was given, because most studies did not confirm either the positive or negative predictive value of EPS for the occurrence of cardiac events at follow-up.^{17,19,20} The debate on the value of EPS in pediatric patients with BrS is still ongoing. Indeed, literature data^{9,12} show that the inducibility of ventricular arrhythmias during EPS failed to identify patients younger than 12 years at risk for AEs during follow-up. As a result, there is no gen-

eral consensus on the prognostic value of EPS in this specific setting.⁷ In our study, EPS was performed in only a small group of patients (20%) with previous episodes of cardiac arrhythmias because we do not routinely use this invasive test in children. However, our data seem to suggest that in these particular patients, EPS could be useful in predicting AEs.

Considerable uncertainty remains regarding the management and outcomes of pediatric patients with BrS. The use of ILR has been reported in pediatric patients to identify occult arrhythmias as well as to accurately assess AEs during symptoms.^{21,22} In the present study, the ILR was safely implanted without adverse events, confirming the usefulness of this tool for guiding management and therapy escalation. Moreover, in our patient cohort, the ILR was effective in symptomatic patients allowing the detection of malignant AEs in 1 patient and avoiding ICD implantation in 3 patients who did not experience malignant AEs.

The indication for ICD implantation is a difficult decision in young patients, and the decision to recommend an ICD should be considered after careful evaluation.

In the study of Gonzalez Corcia et al,²³ inappropriate ICD shocks were reported in 20% of patients because of sVT, noise, and T-wave oversensing. Our experience confirms the high complication rate in very young patients.

Study limitations

The limited number of patients with severe AEs in this study population could have caused a statistical type II error and the lack of identification of some significant associations. In addition, this is a retrospective study that included patients with heterogeneous clinical characteristics. Finally, as already stated, EPS was not performed in all children, but mainly in high-risk patients.

Conclusion

This study reports a unique single-center experience with mid-term follow-up in a pediatric cohort of patients younger than 12 years with a diagnosis of BrS.

Finally, our data suggest that in such a population, (1) a spontaneous type 1 Brugada ECG pattern does not seem to be associated with an increased incidence of episodes of first-degree AV block, premature beats, nonmalignant and malignant AEs, or episodes of syncope compared with drug/fever-induced type 1 ECG pattern; (2) *SCN5A* mutations are associated with the occurrence of malignant AEs; (3) syncope events are correlated with an increased incidence of malignant AEs; (4) the ILR can be an optimal diagnostic option to guide patient management and therapy escalation, particularly in symptomatic patients; and (5) in high-risk patients, EPS could be useful in predicting AEs.

Acknowledgments

We thank Elisa Del Vecchio, MA; for her collaboration in the editorial revision.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2021.06.1177>.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391–1396.
2. Milman A, Andorin A, Gourraud JB, et al. Age of first arrhythmic event in Brugada syndrome: data from the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 patients. *Circ Arrhythm Electrophysiol* 2017;10:e005222.
3. Conte G, Dewals W, Sieira J, et al. Drug-induced Brugada syndrome in children: clinical features, device-based management, and long-term follow-up. *J Am Coll Cardiol* 2014;63:2272–2279.
4. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiet JC. Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol* 2000;86:91–94.
5. Probst V, Denjoy I, Meregalli PG, et al. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* 2007;115:2042–2048.
6. Michowitz Y, Milman A, Andorin A, et al. Characterization and management of arrhythmic events in young patients with Brugada syndrome. *J Am Coll Cardiol* 2019;73:1756–1765.
7. Drago F, Bloise R, Bronzetti G, et al. Italian Association of Arrhythmology and Cardiac Pacing (AIAC) and the Italian Society of Pediatric Cardiology (SICP). Italian recommendations for the management of pediatric patients under twelve years of age with suspected or manifest Brugada syndrome. *Minerva Pediatr* 2020;72:1–13.
8. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36:2793–2867.
9. Oe H, Takagi M, Tanaka A, et al. Prevalence and clinical course of the juveniles with Brugada-type ECG in Japanese population. *Pacing Clin Electrophysiol* 2005;28:549–554.
10. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing Clin Electrophysiol* 2003;26:1551–1553.
11. Andorin A, Behr ER, Denjoy I, et al. Impact of clinical and genetic findings on the management of young patients with Brugada syndrome. *Heart Rhythm* 2016;13:1274–1282.
12. Gonzalez Corcia MC, Sieira J, Pappaert G, et al. A clinical score model to predict lethal events in young patients (≤ 19 years) with the Brugada syndrome. *Am J Cardiol* 2017;120:797–802.
13. Richter S, Sarkozy A, Veltmann C, et al. Variability of the diagnostic ECG pattern in an ICD patient population with Brugada syndrome. *J Cardiovasc Electrophysiol* 2009;20:69–75.
14. Chanavirut R, Makarawate P, Macdonald IA, Leelayuwat N. Autonomic and cardio-respiratory responses to exercise in Brugada syndrome patients. *J Arrhythm* 2016;32:426–432.
15. Song M, Helguera G, Eghbali M, et al. Remodeling of Kv4.3 potassium channel gene expression under the control of sex hormones. *J Biol Chem* 2001;276:31883–31890.
16. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. *Circulation* 2010;121:635–643.
17. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDICTive valuE) registry. *J Am Coll Cardiol* 2012;59:37–45.
18. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol* 2006;17:577–583.
19. Priori SG, Wilde AA, Horie M, et al. Executive summary: HRS/EHRA/APHRS Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;15:1389–1406.
20. Brugada P, Geelen P, Brugada R, Mont L, Brugada J. Prognostic value of electrophysiologic investigations in Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:1004–1007.
21. Avari Silva JN, Bromberg BI, Emge FK, Bowman TM, Van Hare GF. Implantable loop recorder monitoring for refining management of children with inherited arrhythmia syndromes. *J Am Heart Assoc* 2016;5:e003632.
22. Placidi S, Drago F, Milioni M, et al. Miniaturized implantable loop recorder in small patients: an effective approach to the evaluation of subjects at risk of sudden death. *Pacing Clin Electrophysiol* 2016;39:669–674.
23. Gonzalez Corcia MC, Sieira J, Pappaert G, et al. Implantable cardioverter-defibrillators in children and adolescents with Brugada syndrome. *J Am Coll Cardiol* 2018;71:148–157.