Arrhythmic Events in the Young with Brugada Syndrome: Characterization, Management and Risk Factors for Recurrence

Brief title: Arrhythmias in the Young with Brugada Syndrome

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Abstract

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

Objectives. To describe their characteristics and management as well as risk factors for AE recurrence.

Methods: Fifty-seven patients (aged ≤20 years), all with BrS and AEs were divided into pediatric (≤12 years old, n=26) and adolescents (13-20 years old, n=31).

Results: Patients' median age at time of first AE was 14 years, with a majority of males (74%), Caucasians (70%), 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-ECG, inducible ventricular fibrillation at electrophysiologic study and *SCN5A* mutations were present in 26%, 49%, 65%, 28% and 58% of patients, respectively.

The pediatric group differed from the adolescents thru 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 months, respectively. Approximately one third of recurrent AEs occurred on quinidine therapy and among the pediatric group, 60% of recurrent AE 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.

Key words: Brugada syndrome, pediatric, adolescence, quinidine, ablation, *SCN5A* mutation.

Condensed abstract

This study involved 57 young Brugada syndrome patients with an arrhythmic event (AE) who were divided into pediatric (≤12 years old, n=26) and adolescent age (13-20 years old, n=31) subgroups. Each subgroup had unique baseline characteristic features. Both subgroups demonstrate a high AE recurrence rate (64-68%) and approximately one third of recurrent events occurred on quinidine therapy. 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. Considering these risk factors may help in patient management.

Abbreviations:

ACA= aborted cardiac arrest.

AE= arrhythmic event.

AF= atrial fibrillation.

AFL= atrial flutter.

AT= atrial tachycardia.

AV= atrio-ventricular

BrS= Brugada syndrome.

CI= confidence interval.

ECG= electrocardiogram.

EPS= electrophysiological study.

HR= hazard ratio.

ICD= implantable cardioverter-defibrillator.

IQR= Interquartile range

SABRUS= The Survey on Arrhythmic Events in BRUgada Syndrome.

SCD= sudden cardiac death.

SND= sinus node dysfunction.

SVT= supraventricular tachycardia.

VT= ventricular tachycardia

VF= ventricular fibrillation.

Introduction

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 mainly focused on adults who constitute the majority of symptomatic patients (3,4).

Currently, the literature on children and adolescents with BrS and arrhythmic events (AEs) is limited. Among the largest published series of young patients with BrS comprising 30-128 patients, only very few patients (n=1-10) presented as aborted cardiac arrest (ACA) or exhibited an AE during follow-up (n=1-4) (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-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) 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 threefold: 1) to describe the clinical, ECG, electrophysiologic and genetic characteristics of a substantial cohort of young BrS-patients (≤20 years) with documented AE; 2) to compare the characteristics of the pediatric (≤12 years) and adolescent age groups (13-20 years); 3) to describe the management and follow-

up of the young patients ($\leq$20 years) after their first AE and assess possible predictors for AE recurrence.

Methods

Patient selection.

Patients were included if they fulfilled the following two criteria: 1) Presence of a spontaneous or drug-induced typical type 1 Brugada-ECG; 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 which agreed to collaborate in the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS). For the current project, all 23 centers were requested to provide additional baseline and follow-up data (see below) on all their patients aged $\leq$ 20 years who belonged to the original SABRUS cohort. Also, all centers were asked to provide data on any new young BrS patients ($\leq$ 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 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 study was approved by the Institutional Review Board committees of all participating centers.

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 group B, see below); 3) gender;

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 electrophysiologic study (EPS). Protocol of programmed ventricular stimulation was non uniform among the various centers, however it included at least 1 right ventricular site and up to 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 atrio-ventricular (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 V1, V2, and V3 (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 aged ≤ 20 years old. This group of patients was further divided into a pediatric (age ≤ 12 years old) and adolescent groups (age ≥ 13 and ≤ 20 years old).

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 non-proband was defined as a family member of a known BrS-patient.

Genetic analysis: When a *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's 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 [IQR] 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. Log rank test was used to compare event recurrence between the two 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, NY, USA).

Results

Main characteristics of the young BrS group (≤ 20 years) with AE.

Table 1 displays the main characteristics of the young patient group. The cohort comprised 57 patients, median age (IQR) of 14 (3-18) 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 19.6-48% 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 out of 29 (10.3%) of patients who were tested and included ventricular tachycardia (VT) followed by electro-mechanical 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 Supplemental Data for details).

Comparison between the pediatric (age ≤ 12) and adolescent (13 ≤ age ≤ 20) groups.

Main comparative results are displayed in **Table 1**. A higher proportion of females and

Caucasians were noted in the pediatric group as compared to 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 **Supplemental Table 1A-C.** More AEs were

associated with fever in the pediatric group. Pediatric patients were more likely to have

spontaneous type 1 ECG while 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 (AF) (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: AF (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 neurologic sequelae secondary to prolonged resuscitation.

Table 2 summarizes patients' follow-up and management after their first AE.

Out 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 above, another 4 patients (18.1%) died during 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, 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 one. These events occurred without anti-arrhythmic therapy (6 patients) or while on quinidine therapy (5 patients, 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%) **(Supplemental Table 2).** Of the 12 patients with fever-related first AE, 7 out 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 out 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 while 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 AEs 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 months 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 (2 patients

from the pediatric group were excluded from the current analysis since, as stated above,

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 [HR of 5.0

(95% CI, 1.03-23.8, p=0.045)]. Pediatric patients with one or more of the aforementioned

risk factors had a HR of 6.9 (95% CI, 1.9-25.2, p=0.004) for recurrent AE compared to

patient without any of these variables. **Figure 2A** shows Kaplan Meier curve for AE recurrence in pediatric patients with 1 or more risk factors compared to 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). **Figure 2B** shows 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 while it was 105.5 months in patients not carrying the *SCN5A* mutation (P=0.03). All other variables **(Supplemental Table 2A-B)** including gender, 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; (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 literature is relatively small (1). Even more

so in the young population, as attested in SABRUS, where the pediatric group (<16 years) represented a minority of 4.3% (1). In 2007 Probst and colleagues (5) published the first largest pediatric series (age <16 years) that included 30 BrS children. Of this cohort, one 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 19 and 25 years old. 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 to adolescent BrS patients.

An advantage of the current study is the relatively high number of young patients included which enabled to characterize pediatric compared to adolescent patients separately. Among the main differences observed between these 2 groups was the higher proportion of females in the pediatric group as compared to the adolescent group. In addition, this study emphasized our previous observation that an Asian origin was rare amongst 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 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 below). 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 14-26% (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 aged <19 years, and in all their 9 patients (100%) who suffered an AE. Our group previously reported a much lower mutation rate (29.4%) in 201 asymptomatic BrS patients aged <16 years old (13). However, Gonzalez Corcia et al. (8) reported mutations rates of 45% (9 out of 20) in symptomatic BrS patients (most with syncope) compared to mutation rates of 73% (24 out of 33) in asymptomatic patients aged ≤ 25 years old. 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, that 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 40-70% at 10-year follow up with a median time for recurrence more than 24 months (10,21,22). Gonzalez Corcia and colleagues (10) reported a 40% AE recurrence rate in a smaller cohort of 10 BrS patients aged ≤ 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 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; (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 dependent phenotype in these young patients, as

previously also suggested (28). Also, pro-active monitoring during (upcoming, e.g. vaccinations) fever, and anti-pyretic 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 suffered 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 and colleagues (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.

Limitations

The current study is retrospective and observational in nature and therefore any conclusion 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 ($\leq$ 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.

Perspectives

Competency in knowledge: The literature on young patients with BrS and an AE is limited. Gathering the largest series of pediatric and adolescent patients ever reported, enabled us to characterize their baseline profile. More importantly, risk factors for recurrent AE were determined for each age subgroup.

Competency in patient care: A sizable proportion of young patients with BrS and an AE have a very active and malignant disease. ICD implantation may not be enough in these patients and other therapeutic measures should be implemented in patients who have risk factors for recurrent AE.

Competency in patient care: Fever is a medical emergency in pediatric patients with previous fever-related AE. These patients should be admitted to an intensive care unit and treated with urgent antipyretic measures.

Translational outlook: Additional research is needed for defining the best management policy of young children and adolescents with BrS and an AE who have risk factors for arrhythmia recurrence.

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Figure legends

Figure 1: **Kaplan-Meier curve for recurrent arrhythmic event among the pediatric and adolescent patients.** In both age groups a high recurrence AE rate (59.1% and 35.7% at 12-month, respectively, P=0.27) was observed with median time to recurrence of 9.9 months and 27.2 months, respectively.

Figure 2 (Central illustration) A: **Kaplan-Meier curve for recurrent arrhythmic event 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, intra ventricular conduction delay or large S wave in ECG lead I). Patients with risk factors had significantly higher arrhythmic event rate that occurred earlier.

B: **Kaplan-Meier curve for recurrent arrhythmic event among the adolescents with or without *SCN5A* mutation.** As shown, patients with positive mutation had significantly higher event rates that occurred earlier.

Table 1: Comparison between children (age ≤ 12 years) and adolescents (13 ≤ age ≤ 20 years) patients with Brugada syndrome and an arrhythmic event.

		age ≤ 12 n= 26	13≤age≤20 n= 31	P value
Age at AE in years	median (IQR)	3 (1.4, 7.1)	18 (16, 19)	**<0.001**
Gender				
	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
	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
	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)	0.79
	QRS fragmentation	6 (28.6)	11 (40.7)	0.54
	S in lead I	6 (30)	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)	17 (63)	0.4
	AE during test	2 (16.7)	1 (5.9)	0.55

AE=arrhythmic event; AV= atrio-ventricular; BrS= Brugada syndrome; IVCD= intraventricular conduction delay; SCD=sudden cardiac death; VF=ventricular fibrillation.

* data available for 24 children and 28 adolescents.

Table 2: Patients management and follow-up after the first AE.

		age ≤ 12	13 ≤ age ≤20	P value
		n=22	n=28	
Follow up in months	Duration median (range)	39 [0.33-72]	71 [0.27-120]	0.14
	Number of patients with 2nd AE	15 (68.1)	18 (64.3)	0.23
	Fever-related recurrent AE	9 (60)	1 (5.9)	**0.002**
Treatment	Quinidine during part or all FU	8 (36.3)	10 (35.7)	1
Clinical Manifestation of 2nd AE*	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)	N/A
	AE without quinidine	6 (40.0)	12 (66.7)	
	VF storm without quinidine	0 (0)	1 (5.6)	
	Death without quinidine	4 (26.7)	0 (0.0)	

AE = arrhythmic event; FU = follow-up; N/A= not applicable; VF = ventricular fibrillation.

The 2 patients form the pediatric group who died from neurological complications after the first AE are not included in the table.
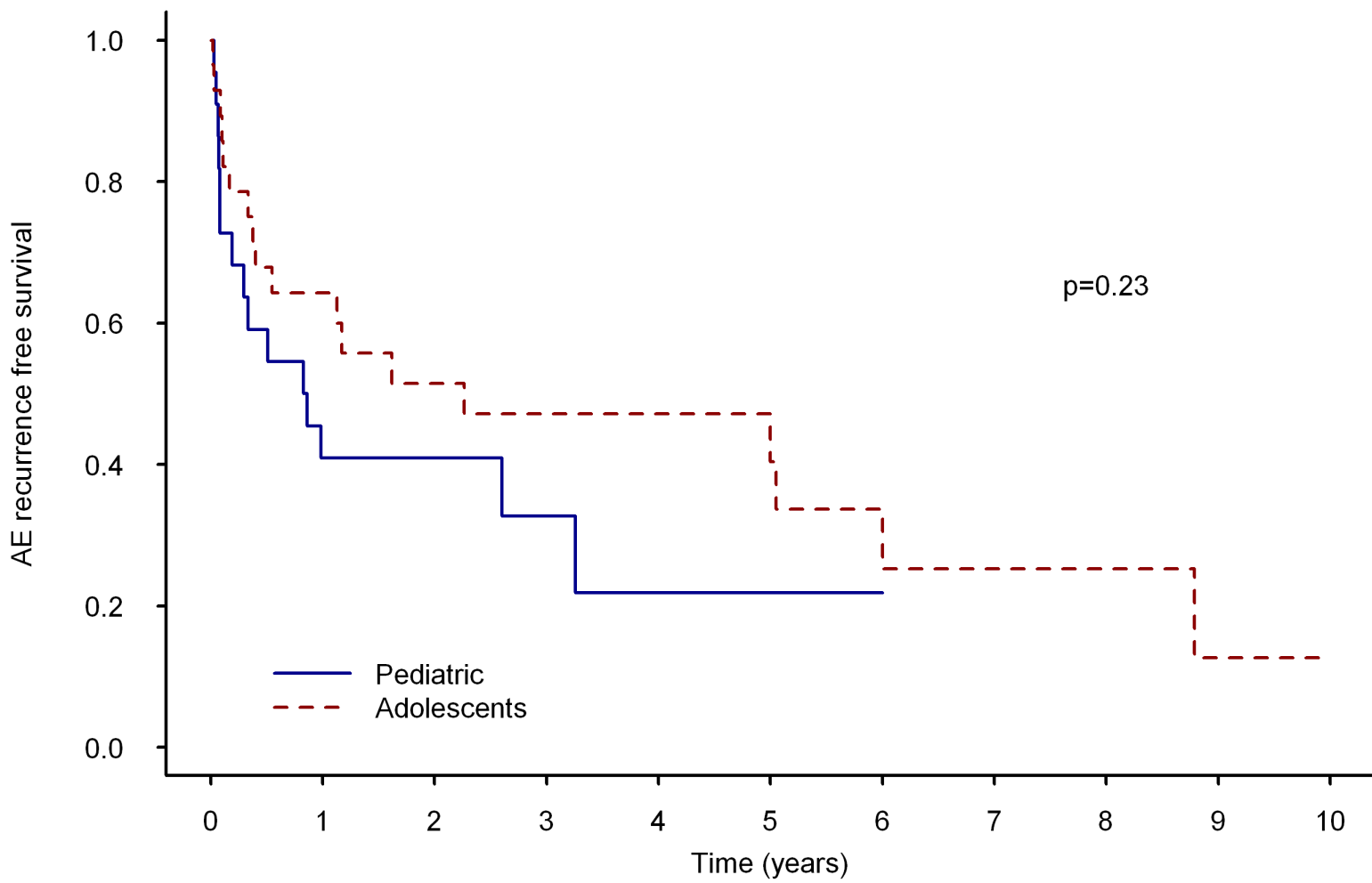
Table 3: Risk factors for recurrent AE

Variable	Event rate with variable*	Event rate without variable**	HR	95% CI	P value
Age ≤ 12					
SND	7/7 (100)	7/14 (50)	3.3	1.1-9.7	0.03
Atrial Arrhythmias	9/9 (100)	6/13 (46)	3	1.07-8.7	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	1.04-9.3	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					
SCN5A mutation	8/9 (89)	3/8 (38)	5	1.03-23.8	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 (%)
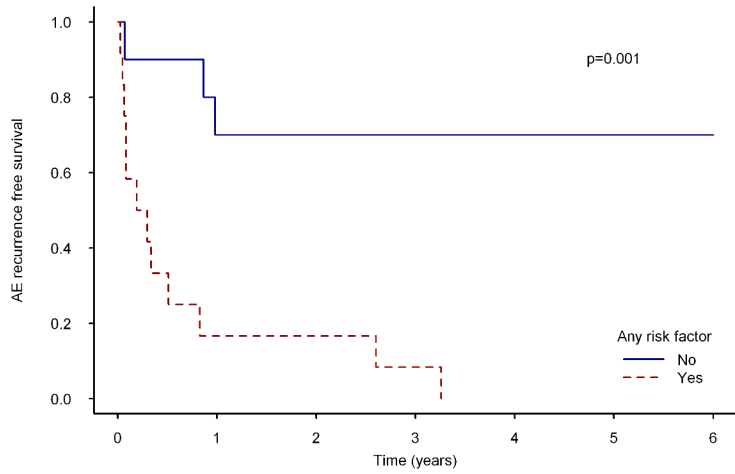
CI = confidence interval; HR = hazard ratio; IVCD = Intraventricular conduction delay (QRS≥110 ms); SND = sinus node dysfunction.

A. Pediatric group

AE recurrence free survival vs Time (years)

p=0.001

Any risk factor
— No
-- Yes

Number at risk:

	0	1	2	3	4	5	6
No	10	7	5	3	2	2	1
Yes	12	2	2	1	0	0	0

B. Adolescent age group

AE recurrence free survival vs Time (years)

p=0.03

— SCN5A -
-- SCN5A +
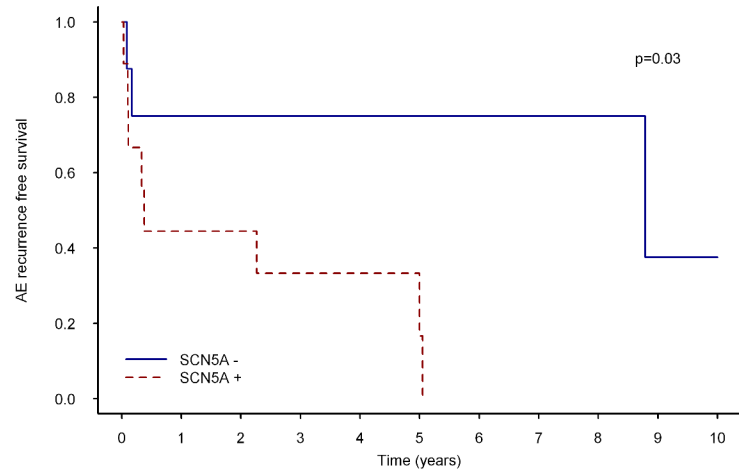
Number at risk:

	0	1	2	3	4	5	6	7	8	9	10
SCN5A -	8	6	5	4	4	3	2	2	2	1	1
SCN5A +	9	4	4	3	2	2	0	0	0	0	0