VOL. 73, NO. 14, 2019
ISSN 0735-1097/$36.00

Letters

Unexpected Risk Profile of a Large Pediatric Population With Brugada Syndrome

The clinical course of Brugada syndrome (BrS) in children and adolescents is incompletely defined due to the rarity of the phenotype in the first decades of life. In 2007, Probst et al. (1) reported the outcome of 30 pediatric patients with 3 years of follow-up, who experienced a 3% annual incidence of major arrhythmias that occurred in symptomatic patients with a spontaneous type 1 electrocardiogram (ECG) pattern. This study concluded that symptomatic BrS children with a spontaneous type 1 ECG have a severe clinical course. One decade later, the same group published a larger cohort of young BrS patients followed up for 4.5 years, reporting an annual incidence of cardiac arrest of 2% among "symptomatic patients" (2). Unfortunately, no information was provided on whether patients experiencing events and labeled as symptomatic had experienced a syncope or a malignant arrhythmia requiring defibrillation. Also, this second study highlighted the high risk of death in young patients with a spontaneous type 1 ECG. Interestingly, in 2017, the message that symptomatic young individuals with spontaneous type 1 are at high risk was reinforced by the Brugada group, who also proposed that patients with multiple electrical abnormalities and either a history of cardiac arrest or a history of syncope should qualify for an implantable cardioverter-defibrillator (ICD) (3).

TABLE 1 Phenotypic Characteristics of the Study Population

	Total Cohort (N = 129)	Spontaneous Type 1 (n = 91)	Drug-Induced Type 1 (n = 38)	p Value*
Demography				
Males	98 (76.0)	69 (76.0)	29 (76.0)	1.00
Probands	92 (71.0)	68 (75.0)	24 (63.0)	0.20
Family history of SCD	14 (11.0)	9 (10.0)	5 (13.0)	0.50
Age at first visit, yrs	11.0 ± 5.9	9.1 ± 5.6	15.7 ± 3.8	<0.001
SCN5A mutation	46 (36.0)	34 (37.0)	12 (32.0)	0.68
Clinical manifestation at presentation				
Aborted cardiac arrest	2 (1.6)	2 (2.0)	0 (0.0)	–
Wide-QRS complex tachycardia	1 (0.8)	1 (1.0)	0 (0.0)	–
Syncope	11 (8.6)	7 (8.0)	4 (11.0)	0.73
Asymptomatic	115 (89.0)	81 (89.0)	34 (89.0)	1.00

Values are n (%) or mean ± SD. *Continuous variables were compared with unpaired Student's *t*-test, and categorical variables were compared with chi-square test.
SCD = sudden cardiac death.

On the basis of current guidelines (4), having survived a cardiac arrest mandates the implantation of an ICD; however, whether such a recommendation applies also to the pediatric population with BrS and with a history of syncope has not been defined. Considering the high rate of complications associated with the use of ICDs in young patients (5), the issue requires attention to avoid unnecessary implantations.

The analysis of our database of prospectively followed individuals with BrS resulted in some interesting observations. Between 2000 and 2018, 129 patients <20 years of age were diagnosed with BrS (Table 1). Overall, 91 of 129 patients (71%) exhibited a spontaneous type 1 ECG pattern, whereas 38 of 129 individuals (29%) were diagnosed after flecainide/ajmaline infusion. Interestingly, 3 of 129 children (2.4%) survived a life-threatening arrhythmic event: 2 aborted cardiac arrests and 1 episode of fast and poorly tolerated wide-QRS complex tachycardia; 11 of 129 patients (8.6%) presented with syncope; and the remaining 115 of 129 patients were asymptomatic. An ICD was implanted in 13 of 129 patients (10%).

During 7.2 ± 4.8 years of follow-up, only 2 individuals, who had survived, respectively, an aborted cardiac arrest and a wide complex tachycardia, had a recurrent life-threatening arrhythmic event that was rescued by defibrillation. Remarkably, no patients who had presented with syncope experienced a cardiac arrest during the follow-up.

Overall, the annual rate of cardiac arrest was 0.2% (95% confidence interval: 0.03% to 0.9%) in the entire population, and 0.3% (95% confidence interval: 0.08% to 1.36%) in patients with a spontaneous type 1 ECG pattern.

Considering the larger size and the longer follow-up of our cohort, we have evidence to amend the current view that pediatric patients with BrS have a high risk of arrhythmic death. The 2 main factors that likely account for the different outcome between the previous cohorts and ours are: 1) the lower percentage of symptomatic patients at diagnosis in

our study (1–3); and 2) previous papers (1,2) have grouped patients with a history of cardiac arrest and patients with a history of syncope within the high-risk "symptomatic" individuals.

The 12.7% annual rate of recurrent life-threatening arrhythmias among survivors of cardiac arrest in our cohort mandates the indication for an ICD in this group. However, the absence of fatal arrhythmias at follow-up in patients who experienced a syncope in our cohort calls for caution before rushing patients to receive an implant. Considering the reported age-dependency of BrS (4), where clinical manifestations appear predominantly in the third and fourth decade, a more conservative approach may be indicated in the pediatric population where quinidine treatment with the implantation of a loop recorder could represent an alternative to the ICD.

Andrea Mazzanti, MD
Paz Ovics, MD
Ayelet Shauer, MD
Stefano Mameli, MD
Maira Marino, RN
Raffaella Bloise, MD
Nicola Monteforte, MD
Cristina Raimondo, MD
Alice Maltret, MD
Carlo Napolitano, MD, PhD
Vincenzo Bagnardi, PhD
***Silvia G. Priori, MD, PhD**

*Molecular Cardiology
IRCCS ICS Maugeri
Via Maugeri, 10
27100 Pavia, Italy
E-mail: silvia.priori@icsmaugeri.it
Twitter: @icsmaugeri

https://doi.org/10.1016/j.jacc.2019.02.021

Please note: This work was supported by the Ricerca Corrente Funding scheme of the Italian Ministry of Health. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Probst V, Denjoy I, Meregalli PG, et al. Clinical aspects and prognosis of Brugada syndrome in children. Circulation 2007;115:2042–8.

2. 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;13:1274–82.

3. 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.

4. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2015;36:2793–867.

5. Celiker A, Olgun H, Karagoz T, et al. Midterm experience with implantable cardioverter-defibrillators in children and young adults. Europace 2010;12:1732–8.

Oral Anticoagulation Therapy and Progression of Calcific Aortic Valve Stenosis

Calcific aortic valve stenosis (AS) is the most prevalent valvular heart disease in high-income countries (1), and currently there is no pharmacotherapy known to prevent its progression. Oral anticoagulants are the benchmark for preventing thromboembolic complications, especially in condition such as atrial fibrillation, which is present in ≤30% of AS patients (2). However, there is little evidence regarding the effect of anticoagulation on the progression of AS. We hypothesized that compared with new oral anticoagulants (e.g., direct oral anticoagulants [DOACs]) or no oral anticoagulant therapy, warfarin therapy is associated with faster AS progression: that is, progressions of peak aortic jet velocity (V_{peak}) on Doppler echocardiography and aortic valve calcification (AVC) score on multidetector computed tomography (MDCT).

We identified 303 patients with at least mild AS (V_{peak} of at least 2.0 m/s and/or aortic valve area <2.0 cm^2) between March 2006 and October 2017. Patients were considered eligible for this study if echocardiography and/or MDCT were repeated after >6 months. Exclusion criteria were history of rheumatic valve disease, endocarditis, more than mild mitral stenosis, severe mitral/aortic regurgitation, left ventricular ejection fraction <50%, and previous valve repair or replacement. Patients who interrupted their anticoagulation therapy or who crossed over (between warfarin and DOAC) throughout the analysis period were excluded. Patients were classified into 3 groups: 1) warfarin; 2) dabigatran, rivaroxaban, apixaban, or edoxaban (DOAC); or 3) no anticoagulant therapy. All patients included in this study were white/Caucasian.

Among the 303 patients (71 ± 12 years, 71% male), 75 were treated with warfarin, 56 were treated with DOAC, and 172 had no anticoagulation therapy. Compared with patients without anticoagulation therapy, those treated with warfarin or DOAC harbored a greater burden of comorbidities, being older (warfarin: 79 ± 8 years vs. DOAC: 75 ± 9 years vs. no anticoagulant: 65 ± 12 years; $p < 0.0001$) and more likely to have hypertension (92% vs. 91% vs. 79%, respectively; $p = 0.01$), atrial fibrillation or flutter (96% vs. 100% vs. 0%, respectively; $p < 0.0001$), renal disease (45% vs. 27% vs. 11%,