Clinical Aspects and Prognosis of Brugada Syndrome in Children

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Background—Brugada syndrome is an arrhythmogenic disease characterized by an ECG pattern of ST-segment elevation in the right precordial leads and augmented risk of sudden cardiac death. Little is known about the clinical presentation and prognosis of this disease in children.

Methods and Results—Thirty children affected by Brugada syndrome who were <16 years of age (mean, 8±4 years) were included. All patients displayed a type I ECG pattern before or after drug provocation challenge. Diagnosis of Brugada syndrome was made under the following circumstances: aborted sudden death (n=1), syncope of unexplained origin (n=10), symptomatic supraventricular tachycardia (n=1), suspicion of Brugada syndrome (n=17). Syncope was precipitated by fever in 5 cases. Ten of 11 symptomatic patients displayed a spontaneous type I ECG. An implantable cardioverter-defibrillator was implanted in 5 children; 4 children were treated with hydroquinidine; and 1 child received a pacemaker because of symptomatic sick sinus syndrome. During a mean follow-up of 37±23 months, 1 child experienced sudden cardiac death, and 2 children received an appropriate implantable cardioverter-defibrillator shock; all of them were symptomatic and had manifested a type I ECG spontaneously. One child had a cardioverter-defibrillator infection that required explantation of the defibrillator.

Conclusions—In the largest population of children affected by Brugada syndrome described to date, fever represented the most important precipitating factor for arrhythmic events, and as in the adult population, the risk of arrhythmic events was higher in previously symptomatic patients and in those displaying a spontaneous type I ECG. (Circulation. 2007;115:2042-2048.)

Key Words: arrhythmia • Brugada syndrome • death, sudden • genetics • ion channels • pediatrics • tachyarrhythmias

Brugada syndrome (BrS) is an inherited arrhythmogenic disorder characterized by a typical ECG pattern consisting of ST-segment elevation in the right precordial leads (V1 through V3) and by an increased risk of sudden cardiac death (SCD) resulting from episodes of polymorphic ventricular tachyarrhythmias (VT).1

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BrS is inherited as an autosomal-dominant trait and has been linked to mutations in the SCN5A gene encoding the α-subunit of the cardiac sodium channel protein.2 To date, genetic mutations are identified in only 20% to 30% of patients with definite or suspected BrS, and all identified mutations (except for a preliminary report) involve the SCN5A gene.3

Diagnosis of BrS revolves around the typical ECG pattern, the so-called type I ECG, which may be present either spontaneously or after provocation test with sodium channel blockers.3,4 The penetrance of the disease is very variable, resulting in heterogeneity of clinical settings, from totally

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asymptomatic individuals to SCD at young age as first presentation. In adults, spontaneous occurrence of a type I ECG and the presence of symptoms are the 2 most important criteria that determine the risk for malignant arrhythmias and sudden death and thus represent an indication for implantation of an implantable cardioverter-defibrillator (ICD).3–8

Despite impressive progress in characterizing BrS in the last 15 years, little is known about the prevalence, diagnostic criteria, and natural history of this disease in the pediatric population. Yet, the disease has been described in children, as in the first article on this syndrome, and it is regarded as potentially linked to SCD in the young.1,3,4,6,9,10

The aim of the present study was to investigate the clinical aspects and genetic background in children (<16 years of age) affected with BrS using data collected from 13 different hospitals in Europe and to identify risk factors for arrhythmic events during an average follow-up period of >3 years.

Methods

Clinical Data

Data were collected from 13 tertiary hospitals in 3 different European countries (the Netherlands, Germany, and France). Inclusion criteria included age <16 years and the presence of a type I ECG either spontaneously or after a provocation challenge with a sodium channel blocker. A type I ECG was defined as a prominent coved ST-segment elevation ≥2 mm or 0.2 mV at its peak, followed (without isoelectric separation) by a negative T wave in ≥2 right precordial leads.3

The study was conducted according to the guidelines for genetic research and was approved by the local ethics committees. Informed written consent was obtained from the parents of each patient who agreed to participate in the study. A total of 30 children were included. Clinical data consisted of sex, date of birth, age and circumstances at diagnosis, presence/absence of symptoms, and treatment (when needed). Moreover, investigation of family history for the presence of BrS in 1 (or more) family members and for occurrence SCD at young age was performed for all patients.

Further clinical examination included 12-lead ECGs at baseline and during drug testing with a sodium channel blocker (n=16) conducted to unmask concealed forms of BrS and performed according to the guidelines of the First Consensus Report.4 The 12-lead ECGs were first analyzed by an expert cardiologist in the referring hospital and then reviewed by 3 electrophysiologists (V.P., A.W., and H.L.M.).

ECG parameters of interest before and after drug provocation test were heart rate, PQ interval, QRS duration, maximal ST elevation (among the precordial leads), and QTc duration (Bazett formula). The choice of sodium channel blocker was determined by drug availability at the participating centers. Either intravenous ajmaline (1 mg/kg body weight) or flecainide (2 mg/kg body weight) was administered.

Underlying structural cardiac abnormalities were excluded in all subjects by physical examination, chest x-ray, and 2-dimensional echocardiography. Laboratory tests were done to exclude electrolyte or metabolic disturbances at the time of ECG recording.

Baseline electrophysiological study (EPS) was performed in 6 children. A maximum of 3 ventricular extrastimuli with a minimum coupling interval of 200 ms were delivered from 2 right ventricular sites unless ventricular fibrillation or a sustained VT was induced. Patient treatment was based on the clinical judgment of the referring cardiologist.

During follow-up, patients were considered to have had an arrhythmic event if sudden death occurred or ventricular tachycardia or fibrillation or an appropriate ICD shock was documented in the ICD-stored electrogram. ECG parameters of the affected patients were compared with those of age-matched family members who were not affected by BrS and were not carriers of the familial SCN5A mutation if known.

Genetic Analysis

Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All 28 exons of SCN5A were amplified by polymerase chain reaction using intronic primers.11 Polymerase chain reaction products were screened for an SCN5A mutation using denaturing high-performance liquid chromatography DNA sequencing. We verified that these DNA variants were disease-causing mutations rather than polymorphisms by generally accepted criteria. These include the following: their presence in highly conserved regions of SCN5A, their absence from 100 control individuals, and when possible, cosegregation with the disease phenotype.

Statistical Analysis

Student t test or the Mann-Whitney test was performed when appropriate to test for statistical differences. A value of P<0.05 was considered statistically significant. When applicable, data are presented as mean±SD.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Demographic, Clinical, and Genetic Characteristics

Demographic and clinical characteristics are summarized in the Table. The study population consisted of 30 patients belonging to 26 different families with a mean age at diagnosis of 8±5 years (median, 7.5 years; range, 0 to 16 years).

Diagnosis of BrS was made under the following circumstances: aborted sudden death (n=1), syncope probably related to arrhythmia (n=10), symptomatic supraventricular tachycardia (SVT; n=1), ECG recorded for other medical reasons that was suspicious for BrS (n=1), and family screening for BrS (n=17). All the symptomatic children (n=11) were the index patients in their respective families.

All patients in the present study showed a type I ECG either spontaneously (n=17; Figure 1) or after drug challenge (n=13). Ten of 11 patients who experienced syncope or SCD had a spontaneous type I ECG (90%). Among the 17 patients with a spontaneous type I ECG, 11 were symptomatic (65%), whereas only 1 of the 13 patients with a drug-induced type I ECG was symptomatic.

No male predominance was observed in the total cohort (17 boys versus 13 girls; P=0.8) or in the symptomatic group (boys, 41%; girls, 31%). The age at diagnosis, on average, was similar between symptomatic and asymptomatic children (6.8±5 versus 8.7±4 years).

In 25 patients, BrS also was present in at least 1 family member (83%), and a positive family history for sudden death was found in 10 of those patients (40%). Among the 10 patients with a positive family history of sudden death, only 2 experienced syncope (20%), whereas 9 were symptomatic (syncope or SCD) among the 15 patients without a family history of sudden death (60%). Genetic screening for mutations in the SCN5A gene was performed in 21 of 30 patients (70%). An SCN5A mutation was found in 15 of 21 patients (71%). A familial history of BrS was found in 14 of the 15 patients with a documented SCN5A mutation.
Circumstances of Syncope and Types of Arrhythmias

Most syncope took place at rest (90%). In 1 case, the syncope occurred during exercise. Episodes of syncope or SCD were associated with fever in 5 of 11 cases (45%; Figure 2). In 2 children, VT with a polymorphic aspect was documented. In 1 child, the polymorphic VT was self-terminating (Figure 3), whereas in the second child, external electric cardioversion was needed. In one 3-year-old girl, a rapid monomorphic tachycardia (240 bpm) with broad QRS, left bundle-branch block morphology, and a left-axis deviation was recorded. A bolus of triphosphate adenosine (10 mg IV) was injected twice without any effect, and she was eventually treated by external electric cardioversion (24 J), which restored normal sinus rhythm and hemodynamic stability.

In 4 cases, an SVT was observed that led to syncope in 3 cases. SVT consisted of atrial flutter in 3 of the 4 patients. In 2 of these patients, important signs of sinus node dysfunction also were documented (Figure 4), leading to pacemaker implantation in 1 symptomatic child. In the remaining 5 cases of syncope, no ECG documentation was available.

Analysis of Baseline ECG Parameters

ECG parameters of our BrS patients were compared with those of 60 age-matched control children belonging to the same families but not affected by BrS and not carriers of the familial SCN5A mutation.

At baseline, PR interval (163±31 versus 144±25 ms; P<0.01), QRS duration (105±17 versus 86±15 ms; P<0.0001), and QTc duration (420±31 versus 406±27 ms; P<0.05) were on average significantly longer in the affected children than in the control group. Maximal ST-segment elevation was also significantly higher (2.3±1.8 versus 0.1±0.1 mm). Furthermore, ST-segment magnitude at base-
Line was more pronounced in the symptomatic (3.5±2.2 mm) than in the asymptomatic (1.7±1.2 mm) children in the study group.

**Drug Challenge**
Drug challenge with intravenous administration of flecainide or ajmaline was performed in 16 of 30 children (Figure 2). All tests resulted in a positive response for BrS, with a significant increase in the amount of ST-segment elevation and the appearance of a coved type I pattern (ST at baseline, 1.5±1.3 mm; ST after drug challenge, 4.3±2.9 mm; P<0.001). No adverse events were recorded. On average, heart rate showed no statistically significant difference before and after drug infusion (77±14 versus 77±14 bpm; P=NS), whereas PR interval, QRS duration, and QTc interval increased significantly (PR, from 164±31 to 190±36 ms, P=0.02; QRS, from 103±15 to 121±40 ms, P=0.05; and QTc, from 418±38 to 461±69 ms, P=0.03).

**Electrophysiological Study**
EPS was performed in 6 children (20%) to test VT/ventricular fibrillation inducibility. In 2 cases, EPS was performed during the workup after episodes of syncope; in 4 cases, it was performed in previously asymptomatic children.

VT/ventricular fibrillation was inducible in 3 patients, 2 of whom (75%) had experienced syncope before the EPS. During the follow-up, no arrhythmic event occurred in the patients with a negative EPS, whereas 1 of 3 patients with a positive EPS experienced an arrhythmic event during follow-up.

**Follow-Up**
An ICD was implanted in 5 children. Four were symptomatic, and 1 was asymptomatic but had a positive EPS. Four of 5 children implanted with an ICD had a spontaneous type I ECG (and 3 of them had experienced syncope). Pharmacological therapy with quinidine was started in 4 children. Two were symptomatic (syncope), and 2 were asymptomatic; all of them had a spontaneous type I ECG. A pacemaker was implanted in a male child at 11 years of age because of a symptomatic sick sinus syndrome. He also had shown a type I ECG pattern spontaneously.

During a mean follow-up of 37±23 months, 3 children experienced arrhythmic events (1 sudden death, 2 appropriate ICD shocks resulting from ventricular fibrillation occurring at...
Discussion

SCD is a tragedy at any age but is even more dramatic during childhood and adolescence. Population-based reports show an age-specific rate of sudden death of 1.3 to 4.3 per year per 100,000 inhabitants, and SCD accounts for 19% of the sudden deaths in children between 1 and 13 years of age.

BrS is considered mainly a disease of the young male adult, with a reported mean age at sudden death of 40 years. Initially considered a rare clinical syndrome, BrS is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts. To date, the prevalence of the BrS phenotype in children remains poorly defined. Japanese studies have found a prevalence/incidence of 0.0098%, which is much lower than in the adult population (0.14% to 0.7%).

In their initial description of the disease, Pedro and Joseph Brugada reported the cases of 3 affected children; at the time of diagnosis, 2 children were 2 years of age and 1 child was 8 years old. They all suffered from malignant arrhythmias. Since then, several authors have reported isolated cases of BrS in children, but studies on a large scale are lacking.

In a longitudinal follow-up study of a large family with an SCN5A-related overlap syndrome (which included right precordial ST-segment elevation), the Brugada phenotype appeared significantly later in childhood than the QT prolongation.

The present study was conducted in a population of 30 affected individuals <16 years of age (from 13 different European institutions). In these centers, >800 adult patients with BrS have been seen, showing that BrS in children is very rare compared with the adult population. More than half (17 of 30) of these pediatric cases were diagnosed during family screening, but 11 were index patients identified after a syncopal episode, confirming that BrS also can manifest at a very young age.

In contrast to what is observed in adult patients affected with BrS, no male predominance in the number of symptomatic individuals was found in our patient population. The molecular mechanisms underlying sex-related differences in electrophysiology are poorly understood. However, Matsuo et al described 2 BrS patients whose ST-segment elevation normalized after orchietomy prescribed for the treatment of prostate cancer. This demonstrates the major role of androgens in the occurrence of BrS. Because levels of testosterone are low in children of both sexes, it is probably not surprising that we failed to identify a male predominance in this population with a mean ± SD age of 8.2 ± 5 years.

The role of fever as a precipitating factor for ventricular arrhythmias in BrS has been recognized. In our study, nearly half of the syncopal events were precipitated by fever illnesses. This is not surprising considering the high frequency of pyrexial episodes in children. One of the current theories explaining the ECG alterations seen in BrS is based on an imbalance between the depolarizing and the repolarizing currents during the early repolarization phase of the action potential, mainly in cells expressing a large transient outward Ito current such as the epicardial cells of the right ventricle. It has been shown that mutations responsible for BrS alter the temperature sensitivity of fast inactivation of the sodium channel. Other studies have shown that the temperature-dependent properties of wild-type sodium channel itself also might lead to the typical BrS characteristic during fever. The exact mechanism by which fever triggers arrhythmias in BrS remains unknown.

In the study of Pasquier et al, temperature-dependant modifications of ion channel properties or expression were proposed as a potential mechanism to initiate ventricular arrhythmia by facilitating spontaneous activity within the right ventricular outflow tract or the Purkinje system. In any case, our study emphasizes the importance of fever as a precipitating factor for arrhythmic events, especially in
children. For this reason, we recommend that parents be instructed to bring these children to the hospital for cardiac evaluation, ECG, and monitoring of cardiac activity during febrile illnesses if needed. Moreover, efforts to prevent (with vaccinations, when possible), promptly recognize, and treat febrile illnesses in affected children (reduce temperature and cure the underlying disease) have to be made.

Atrial fibrillation and atrial flutter are frequently described in the BrS population. Although this type of arrhythmia is very uncommon in children without structural heart disease, 13% of the patients in our study were affected by this arrhythmia. This is similar to the reported prevalence in the adult BrS population. More surprisingly, half of these young patients also are affected by sinus node dysfunction, which required pacemaker implantation in 1 patient. Screening of the SCN5A gene was performed in 2 of the 4 patients affected by SVT, and a mutation was identified in both cases. SCN5A mutations have already been described in patients affected by sick sinus syndrome or atrial flutter.

Although the role of INa in the sinus node has been debated, it is now well established that sodium channels contribute to sinus node pacemaking in mammals. In the population described here, the proportion of patients carrying a SCN5A mutation is far higher than usually described in BrS (20% to 30%). This finding can be explained by the following explanations. First, family screening, especially in young children, is performed more often when the genetic defect is known. Second, in 3 families, several children belonging to the same family and carrying the same SCN5A mutation were included in the study.

Predictors of Outcome
In our study, all but 1 symptomatic patient (10 of 11) exhibited a spontaneous type I ECG, and the proportion of symptomatic patients was far higher than usually described in BrS (59%) than in patients with a type I ECG only after drug challenge (7%). Although no side effects were observed during sodium blocker administration in the present study, further data are needed to determine whether asymptomatic children with a normal basal ECG during family screening should undergo drug testing. Certainly, the spontaneous presence of a type I ECG was frequently associated with syncope in our study and has to be considered a condition at high risk of arrhythmic events.

Therapeutic Approach in Children Affected by BrS
ICDs were implanted in 5 children (16%) in our study. The majority of them (80%) had a history of syncope. The percentage of children who underwent ICD implantation is lower than in the adult population. This is not surprising because ICD implantation is associated with significant morbidity in childhood and requires lifetime replacement. However, 2 of 4 symptomatic children treated with an ICD received an appropriate shock during a follow-up of 37 months, demonstrating that ICD implantation in symptomatic BrS children is a very effective therapy.

Hydroquinidine has been shown to be a good alternative to ICD implantation in adult BrS patients. In our study, 4 children received hydroquinidine. All of them were high-risk patients, having displayed a type I ECG spontaneously. Moreover, 2 of them had had syncopal events with a documented VT and SVT, respectively. No serious side effects occurred under quinidine, and considering the total absence of symptoms in these patients during a mean follow-up of 28 months, we can affirm that quinidine represents a good alternative to ICD implantation in younger BrS patients who are at risk for development of malignant arrhythmias. Quinidine can be used safely until adult age and posture are achieved. Still, given the small number of patients, studies on a larger scale and with a longer follow-up are needed to confirm these observations.

Conclusions
We present here the results of the largest series, to the best of our knowledge, of children affected by BrS. As in adults, the risk of arrhythmic events in children affected by BrS is high in symptomatic individuals, especially when a spontaneous type I ECG is displayed. Conversely, the prognosis of BrS in asymptomatic children and in children in whom the typical BrS ECG pattern appears only after drug challenge seems to be favorable. In addition, in children affected by BrS, febrile illness represents the most important precipitating factor for arrhythmic events. Accordingly, we believe that the management strategy for children affected by BrS should include prompt recognition and treatment of febrile illnesses with antipyretics. We further recommend that affected patients be instructed to come to the hospital when febrile for an ECG and for rhythm observation when needed. ICD implantation in children, despite being more complex compared with adults, efficiently prevents SCD in symptomatic BrS children. Quinidine also has been shown to be effective during this relatively short follow-up and can be proposed as a valid alternative or as a bridge to ICD implantation.

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Disclosures
None.

References


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