Clinical Aspects and Prognosis of Brugada Syndrome in Children


Circulation 2007; 115:2042-8
Abstract

Introduction: 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 (SCD). Little is known about clinical presentation and prognosis of this disease in children.

Methods and Results: Thirty children affected by Brugada syndrome, younger than 16 years of age (mean 8 ± 4 years) were included. All patients displayed a type I ECG pattern before or after drug challenge. Diagnosis of Brugada syndrome was made under the following circumstances: 1) aborted sudden death (n=1); 2) syncope of unexplained origin (n=10); 3) symptomatic supraventricular tachycardia (n=1); 4) suspicious ECG (n=1); 5) family screening for 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 (ICD) 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 death and 2 children received an appropriate ICD shock; all of them were symptomatic and had manifested a type I ECG spontaneously. One child had an ICD infection which required explantation of the defibrillator.

Conclusion: In the largest population of children affected by Brugada syndrome described to date, fever represented the most important trigger 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.
Introduction

Brugada syndrome is an inherited arrhythmogenic disorder characterized by a typical ECG pattern consisting of ST-segment elevation in the right precordial leads (V1-V3) and by an increased risk of sudden cardiac death (SCD), resulting from episodes of polymorphic ventricular tachyarrhythmias (VT). Brugada syndrome is inherited as an autosomal dominant trait and has been linked to mutations in the \textit{SCN5A} gene, encoding the \(\alpha\)-subunit of the cardiac sodium channel protein. To date, genetic mutations are identified in only 20\% to 30\% of the patients with definite or suspected Brugada syndrome, and all identified mutations (except for a preliminary report) involve the \textit{SCN5A} gene.

Diagnosis of Brugada syndrome revolves around the typical ECG pattern, the so-called type I ECG, which can be present either spontaneously or after provocation test with sodium channel blockers. The penetrance of the disease is very variable resulting in heterogeneity of clinical settings, from totally 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 two most important criteria that determine the risk for malignant arrhythmias and sudden death and, as such, represent an indication for implantation of implantable cardioverter/defibrillators (ICD). Despite impressive progress in characterization of Brugada syndrome 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 is described in children already in the first paper on this syndrome and is regarded as potentially linked to SCD in the young.

Moreover, ICD implantation, the only effective way to prevent SCD in high risk Brugada syndrome patients, is associated with serious co-morbidity in children. The aim of the present study was to investigate clinical aspects and genetic background in children (< 16 years of age) affected with Brugada syndrome, using data collected from 13 different hospitals in Europe and to identify risk factors for arrhythmic events, during an average follow-up period of more than 3 years.
Chapter 5.1

Methods

Clinical Data
Data were collected from 13 tertiary hospitals in three different European Countries (the Netherlands, Germany and France). Inclusion criteria consisted of: 1) age < 16 years 2) 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 $\geq 2$mm or 0.2mV at its peak followed (without isoelectric separation) by a negative T-wave in two or more right precordial leads $^3$. The study was conducted according to the guidelines for genetic research and approved by the local ethical committees. Informed written consent was obtained from the parents of each patient who accepted to participate in the study.

A total of 30 children were included. Clinical data consisted of gender, date of birth, age and circumstances at diagnosis, presence/absence of symptoms and treatment (when needed). Moreover, investigation of family history for presence of Brugada syndrome in one (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 in order to unmask concealed forms of Brugada syndrome and according to the guidelines of the First Consensus Report $^3$.

The 12-lead ECGs were first analyzed by an expert cardiologist in the referring hospital and then revised by three electrophysiologists (V.P., A.W. and H.T).

ECG parameters of interest, before and after drug provocation test were: heart rate (HR), PQ interval, QRS duration, maximal ST elevation (the largest amount of ST segment elevation among the precordial leads) and QTc duration (Bazett formula).

The choice of the sodium channel blocker was determined by the availability of the drug in the participating centres. Either intravenous ajmaline (1mg/kg body weight), or flecainide (2mg/kg body weight) was administered.

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

Baseline electrophysiologic study (EPS) was performed in 6 children. A maximum of 3 ventricular extrastimuli with a minimum coupling interval of 200 ms were delivered from two right ventricular sites unless ventricular fibrillation or a sustained ventricular tachyarrhythmia was induced.

Patient treatment was based on the clinical judgement 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. Electrocardiographic parameters of the affected patients were compared with those of age-matched family members who were not affected by Brugada syndrome 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 utilizing intronic primers \(^\text{10}\). Polymerase chain reaction products were screened for SCN5A mutations 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 in 100 control individuals and, where possible, co-segregation with the disease phenotype.

Statistical Analysis
Student \( t \) test or the Mann-Whitney test was performed, when appropriate, to test for statistical differences. A \( p \)-value < 0.05 was considered statistically significant. When applicable, data are presented as mean \( \pm \) SD.
Chapter 5.1

Results

Demographic, Clinical and Genetic Characteristics
Demographic and clinical characteristics are summarized in the table (see below).

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 Brugada syndrome was made under the following circumstances: 1) aborted-SCD (n=1); 2) syncope of unexplained origin (n=10); 3) symptomatic supraventricular tachycardia (SVT) (n=1); 4) ECG recorded for other medical reasons, that was suspicious for Brugada syndrome (n=1); 5) family screening for Brugada syndrome (n=17).

Figure 1: Twelve lead ECG recorded in a 1-year-old child after a syncopal episode, occurred during fever. In the right precordial leads V1-V2, a type 1 pattern is present.
All the symptomatic children (n=11) were the index patients of their respective families. All patients of the study have 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 (7%; p<0.001).

No male predominance was observed in the total cohort (17 boys vs. 13 girls), or in the symptomatic group (percentage of symptomatic boys 41%; girls 31%). The age at diagnosis, on average, was similar between symptomatic and asymptomatic children (6.8 ± 5 vs. 8.7 ± 4 years). In 25 patients, Brugada syndrome was also 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 SCD, 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 SCN5A gene was performed in 21 out of 30 patients. A SCN5A mutation was found in 15 of 21 patients (71%). A familial history of Brugada syndrome was found in 14 out of the 15 patients with a documented SCN5A mutation.

Figure 2: Representation of the right precordial leads V1 and v2 of a basal ECG (left) and an ECG taken during a febrile episode in a 5-year-old child. During fever (right), ST segment elevation is accentuated, and coved type morphology is displayed in lead V2.
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 5/11 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 electrical 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 electrical 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.
SVTs consisted of atrial flutters in 3 out of the 4 patients. In 2 of these cases, important signs of sinus node dysfunction were also documented (Figure 4) leading to pacemaker implantation in 1 symptomatic child. In the remaining 5 cases of syncope, no electrocardiographic documentation was available.

Figure 3: Three-lead ECG showing self-terminating polymorphic VT in a 1-year-old patient who experienced syncope.
Figure 4: (A) ECG registration showing an atrial flutter (common type) with various degrees of AV block recorded in an 11 year-old child hospitalized after an episode of syncope. (B) After conversion to sinus rhythm the ECG showed signs of severe sinus node dysfunction, prolonged PQ, RBBB configuration with ST segment elevation (type I ECG) in leads V1 and V2. A truncation SCN5A mutation (p.Ala1223ProfsX6) was identified in this patient and in his affected mother.
# Table: Demographic and Clinical Characteristics

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<th>Gender</th>
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<th>Reason of evaluation</th>
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<th>Symptoms triggered by fever</th>
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<th>Family history of BrS</th>
<th>Baseline ECG*</th>
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*F screening indicates family screening. Poly: polymorphic, Mono: monomorphic ventricular tachycardia. PM: pace maker. App shock indicates appropriate shock. *Types of repolarization patterns have been classified as described in the first Consensus Report on Brugada syndrome.*
### Children with Brugada Syndrome

#### Analysis of Baseline ECG Parameters

ECG parameters of our Brugada syndrome patients were compared with those of 60 age-matched control children belonging to the same families, but not affected by Brugada syndrome and not carriers of the familial SCN5A mutation. At baseline, PR interval (163 ± 31 vs. 144 ± 25 ms; p<0.01), QRS duration (105 ± 17 vs. QRS 86 ± 15; p<0.0001) and QTc duration (406 ± 27 ms vs. 420 ± 31 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 vs. 0.1 ± 0.1 mm).

Furthermore, ST segment magnitude at baseline was significantly more pronounced in the symptomatic (3.5 ± 2.2 mm) than in the asymptomatic (1.7 ± 1.2 mm; p<0.01) children in the study group.

#### Drug Challenge

Drug challenge with intravenous administration of flecainide or ajmaline was performed in 16/30 children (Figure 2). All tests resulted in a positive response for Brugada syndrome, with a significant increase in the amount of ST segment elevation and 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 differences before and after drug infusion (77 ± 14 vs. 77 ± 14 bpm, p=NS), while PR interval, QRS duration and QTc interval increased significantly (PR, from 164 ± 31 ms to 190 ± 36 ms; p=0.02; QRS, from 103 ± 15 ms to 121 ± 40 ms p=0.05; and QTc from 418 ± 38 ms to 461 ± 69 ms, p=0.03).

#### Electrophysiological Study

EPS was performed in 6 children (20%) to test VT/VF inducibility. In 2 cases, EPS was performed during work-up after episodes of syncope and in 4 cases in previously asymptomatic children. VT/VF was inducible in 3 patients, two of whom had experienced syncope before the EPS. During the follow-up, no arrhythmic event occurred in the patients with a negative EPS whereas 1 out 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 one 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 have 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 boy at 11 years of age because of symptomatic sick sinus syndrome. He also had shown a type I ECG pattern spontaneously.
During a mean follow-up of $37 \pm 23$ months, 3 children experienced arrhythmic events (1 sudden death and 2 appropriate ICD shocks resulting from ventricular fibrillation occurring at rest). Both patients who received an appropriate ICD shock were symptomatic (syncope) and had manifested a spontaneous type I ECG. The patient that died suddenly had been initially identified at 1 year of age because of symptomatic SVT and spontaneous type I ECG. He died suddenly one year later during a febrile episode. The ECG is missing and no post-mortem examination was performed.
Moreover, one inappropriate ICD shock was recorded. In one case, ICD implantation was complicated by an ICD pocket infection, which led to device removal.
No arrhythmic events or recurrence of symptoms were observed in the patients treated with hydroquinidine during a mean follow-up of $28 \pm 24$ months. The treatment was well tolerated. A type I ECG was seen intermittently in 3 patients and constantly in 1 patient while on quinidine.

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 1.3-4.3 per year per 100,000 inhabitants and SCD account for 19% of sudden deaths in children between 1 and 13 years. Brugada syndrome 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, Brugada syndrome is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in individuals with structural normal hearts. To date, the prevalence of the Brugada syndrome phenotype in children remains poorly defined. Japanese studies have found a prevalence/incidence of 0.0098% which is much lower than in 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 of malignant arrhythmias. Since then, several authors have reported isolated cases of Brugada syndrome 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-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 centres, > 800 adult patients with Brugada syndrome have been seen, showing that Brugada syndrome in children is very rare, compared to the adult population.

More than half (17 of 30) of these pediatric cases were diagnosed during a familial screening, but 11 were index patients identified after a syncopal episode confirming that Brugada syndrome can manifest also at a very young age.

In contrast to what is observed in adult patients affected with Brugada syndrome, 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 two Brugada syndrome patients whose ST segment elevation normalized after orchiectomy, performed for the treatment of prostate cancer. This demonstrates the role of androgens in the occurrence of Brugada syndrome. 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 age of 8 ± 5 years.
The role of fever as a precipitating factor for ventricular arrhythmias in Brugada syndrome has been widely 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 the Brugada syndrome 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 epicardial cells of the right ventricle. It has been shown that mutations responsible for Brugada syndrome 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 might also lead to the typical Brugada syndrome characteristic during fever. The exact mechanism by which fever triggers arrhythmias in the Brugada syndrome remains unknown. In the study of Pasquie et al., temperature-dependent 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 trigger 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 illness. 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 flutters are frequently described in the Brugada syndrome 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 Brugada syndrome population. More surprisingly, half of these young patients are also 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.
Children with Brugada Syndrome

SCN5A mutations have already been described in patients affected by sick sinus syndrome or atrial flutter. Although the role of I_{Na} 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 Brugada syndrome (20 to 30%). This can be explained by the following explanations. Firstly, family screening is performed more often when the genetic defect is known, especially in young children. Secondly, in three 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 one symptomatic patient (10 of 11) exhibited a spontaneous type I ECG and the proportion of symptomatic patients was far higher in the children with a spontaneous type I ECG (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 baseline ECG during familial screening should undergo drug testing. For sure, 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 Brugada Syndrome

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 an adult population. This is not surprising as 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 appropriated shock during a follow-up of 37 months, demonstrating that ICD implantation in symptomatic Brugada syndrome children is a very effective therapy.
Hydroquinidine has been shown to be a good alternative to ICD implantation in adult Brugada syndrome 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 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 Brugada syndrome patients who are at risk for development of malignant arrhythmias. Quinidine can be used safely until adult age is reached. 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 Brugada syndrome. As in adults, the risk of arrhythmic events in children affected by Brugada syndrome is high in symptomatic individuals, especially when a spontaneous type I ECG is displayed. Conversely, the prognosis of Brugada syndrome in asymptomatic children and in children in whom the typical Brugada syndrome ECG pattern appears only after drug challenge seems to be favourable. In addition, in children affected by Brugada syndrome, febrile illness represents the most important precipitating factor arrhythmic events. Accordingly, we believe that the management strategy for children affected by Brugada syndrome 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 to in adults, efficiently prevents SCD in symptomatic Brugada syndrome children. Quinidine also has been shown to be effective during this relatively short follow-up and can be proposed as a valid alternative or a bridge to ICD implantation.
Reference List


Chapter 5.1


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