Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population
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Chapter 7

The Diagnostic and Therapeutic Aspects of Loss-of-Function Cardiac Sodium Channelopathies in Children

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Heart Rhythm (provisional accept)
Abstract

Background and Objective: Loss-of-function sodium channelopathies manifest as a spectrum of diseases including Brugada Syndrome (BrS) and cardiac conduction disease. This study analyzes the diagnostic and therapeutic aspects of these disorders in children.

Methods: Patients aged ≤16 years with genetically confirmed loss-of-function sodium channelopathies (SCN5A mutation), presenting with cardiac symptoms, positive family-history and/or abnormal ECG, were included in the study. Abnormal ECG consisted of Type 1 BrS ECG and/or prolonged conduction intervals (PR interval/QRS duration >2 standard deviations for age).

Results: Among the study cohort (n=33, age 6±5 years, 58% males, 30% probands), 14 (42%) patients were symptomatic, presenting with syncope (n=5), palpitations (n=1), supraventricular arrhythmias (n=3), aborted cardiac arrest (n=3), and sudden cardiac death (n=2). Heart-rate was 91±26 bpm, PR interval 168±35 ms, QRS duration 112±20 ms and QTc 409±26 ms. Conduction intervals were prolonged in 28 (85%) patients; six of these patients also had spontaneous Type 1 BrS ECG. Eight fever-associated events occurred in six patients, and two of these were vaccination-related fever episodes. Treatment included aggressive antipyretics during fever episodes in all patients; antiarrhythmic treatment included ICD (n=4), pacemaker (n=2), and beta-blockers, either alone (n=3) or in combination with device (n=2). During follow-up (4±4 years), two previously symptomatic patients had monomorphic VT; there were no deaths.

Conclusions: Loss-of-function sodium channelopathies manifest at an early age with fever and vaccination as arrhythmia-triggers. Conduction delay is the commonest finding in affected patients. Beta-blockers have a role in preventing tachycardia-induced arrhythmias; ICD should probably be reserved for severe cases.
Introduction

Loss-of-function cardiac sodium channelopathies are caused by mutations in the gene encoding the α-subunit of the sodium channel (SCN5A). They manifest as a spectrum of diseases including Brugada Syndrome (BrS), cardiac conduction disease, familial atrial fibrillation and sick sinus syndrome. The clinical scenario in affected individuals ranges from absence of symptoms to sudden cardiac death (SCD), with syncope and arrhythmias being the commonest presentations. Initially thought to be diseases of young adult men, BrS and related phenotypes are now being diagnosed in infants and very young children as well. In fact, 10%-15% of unexplained deaths in infants (sudden infant death syndrome, SIDS) is attributed to sodium channelopathies. Due to the relative rarity of these disorders in the pediatric cardiology practice, literature on the clinical characteristics and the diagnostic and therapeutic aspects in this patient population is sparse.

The characteristic electrocardiogram (ECG) of BrS (Type 1 ECG), a coved-type ST segment elevation in the anterior precordial leads (V1 to V3), may be seen either spontaneously or after sodium channel blockade, in patients with structurally normal hearts. SCN5A mutations are detected in about a quarter of BrS patients, with a higher incidence of mutations among familial than sporadic cases. However, as loss-of-function cardiac sodium channelopathies are a spectrum of diseases, very young children may present with rapid ventricular tachycardia (VT) and have prolonged conduction intervals. Fever, an established arrhythmia-trigger in BrS, often plays a role in unmasking the underlying genetic disorder in young patients. With family-screening becoming an integral component of managing patients with cardiac channelopathies, more and more young asymptomatic mutation-carriers are being identified. The purpose of this study was to study the clinical presentation and the diagnostic and therapeutic aspects of loss-of-function cardiac sodium channelopathies in children.

Methods

Study Subjects

Patients from 5 tertiary referral hospitals in The Netherlands and Germany, managed between January 1995 and January 2012, were included. Study subjects (n=33) were patients aged ≤16 years at presentation who were subsequently diagnosed with loss-of-function sodium channelopathy defined as genetically confirmed loss-of-function SCN5A mutation(s). The subjects had presented with either (a) pertinent cardiac symptoms and/or an abnormal ECG, or (b) for family-screening of this spectrum of diseases. Pertinent cardiac symptoms included syncope, palpitations, arrhythmias, aborted cardiac arrest (ACA) and SCD. Abnormal ECG consisted of Type 1 BrS ECG and/or prolonged conduction intervals (PR interval/QRS duration >2 standard deviations for age). The absence of underlying structural heart disease and metabolic and electrolyte disturbances at presentation was confirmed in all patients by echocardiography and laboratory investigations, respectively. Four patients were known with congenital heart disease at the time of evaluation for channelopathies.
Data Collection

Demographic and clinical parameters including gender, age at presentation, nature of presenting symptoms, temporal association of symptoms to any unusual events or illnesses, past medical history and relevant family history were retrieved. Systematic examination of the earliest available resting ECG was performed and the following parameters were documented: heart rate (HR), PR interval, QRS duration, heart-rate corrected QT interval (QTc, Bazett’s formula), presence of Type 1 BrS ECG pattern, and arrhythmias if any. Results of genetic testing were recorded, noting in particular the nature and the number of SCN5A mutations in each patient. Mutations were grouped as those causing premature truncation of proteins (T mutation), missense mutations with >90% loss of channel function (M-inactive mutation) and missense mutations with ≤90% loss of channel function (M-active mutation), according to criteria defined before.8

Follow-up duration, details of antiarrhythmic treatment including pharmacological therapy and device therapy such as implantable cardioverter defibrillator (ICD) and pacemaker, and of other treatment provided (such as radiofrequency ablation), and occurrence of pertinent cardiac symptoms during follow-up, were documented.

The study protocol was approved by the scientific committees of each of the participating centres.

Statistical Analysis

Continuous variables are presented as mean ± SD and analysed by t-test. Categorical variables are presented as number of patients (n) and percentage (%) and analysed by χ² test.

Results

Clinical Characteristics

Patients included in the study (n=33) came from 24 families. Age at presentation was 6±5 years (range 0-16.7 years, median age 4.8 years) and a slight male predominance (n=19, 58%) was present. The study cohort consisted of 10 (30%) probands, and 23 (70%) patients had presented for family-screening (Figure 1A). The distribution of symptoms among symptomatic (n=14, 42%) cases is shown in Figure 1B. The cardiac symptoms/arrhythmias in the study subjects at presentation were as follows. Atrial flutter, sinus bradycardia and sinus pauses were observed in a 5-month old female index patient and in 3-year old male during family-screening. A 5-year old male presented with symptomatic supraventricular tachycardia (SVT) that responded to intravenous adenosine treatment. Broad-complex tachycardia requiring defibrillation and resuscitation occurred in a male neonate at birth and in a 4-month old female during a fever episode respectively; ventricular fibrillation (VF) was successfully aborted in a 10-year old female with history of recurrent syncope since infancy. SCD occurred in two patients: in a 3-month old male presenting with refractory broad-complex tachycardia on the day following vaccination; and in a female patient born with a conduction disorder which worsened during infancy culminating in intractable ventricular arrhythmias and death at the age of 1 year.
ECG Features
Heart rate of the subjects was 91±26 bpm, PR interval 168±35 ms, QRS duration 112±20 ms and QTc 409±26 ms. Conduction intervals were prolonged in 28 (85%) patients; in six of these patients, spontaneous Type 1 BrS ECG was present (Figure 2). All but one patient with Type 1 ECG were males. Sodium channel blockade (with flecainide) was performed in two asymptomatic patients with family history of BrS, and was negative. Electrophysiological study was performed in two infants presenting with ACA; progressive widening of the QRS complex accompanied by hemodynamic instability was observed in both patients during atrial pacing with increasing cycle length. The clinical and ECG characteristics of symptomatic and asymptomatic patients were comparable, except for QRS duration which was significantly longer among symptomatic patients (121 ± 22 ms vs. 106 ± 16 ms, p=0.03).

Nature of SCN5A Mutation
Single SCN5A mutations were present in 26 (79%) patients and double SCN5A mutations in seven (21%) patients. Of the 22 SCN5A mutations in the study patients, eleven were T mutations, four were M-inactive mutations, three were M-active mutations, three were missense mutations of unknown functional significance, and one was a polymorphism (Table 1). The nature of SCN5A mutations in relation to occurrence of cardiac events is shown in Figure 3. Cardiac events were seen to occur more often in patients with double mutations and T /M-inactive mutations than in patients with M-active mutations. Compound heterozygosity was diagnosed in two families: post-mortem genetic testing in a male infant revealed two SCN5A mutations.
which were subsequently identified in his sibling during the neonatal period; a male neonate presenting with ACA was found to be a compound heterozygote and his older sister who had died at the age of one year was subsequently identified to have the same mutations by post-mortem genetic testing.9

**Follow-Up and Treatment**

The follow-up duration was $4 \pm 4$ years (range 0.1-16.3 years, median 2.7 years). Families of all patients were counselled on the importance of aggressive antipyretic measures and on the need to report to the hospital for ECG monitoring during fever episodes, and were given information on the drugs to be avoided. Eight patients had at least one ECG recorded in hospital during fever. In three previously asymptomatic patients, worsening cardiac conduction delay and/or increase in ST-segment elevation were observed during admission with fever (Figure 4). In two of these patients, apart from antipyretics, beta-blockers were administered orally until fever subsided.

One or more treatment modalities were employed in 11 (33%) of the patients. ICD (n=4), pacemaker (n=2), beta-blockers, either alone (n=3) or in combination with device therapy (n=2), and radiofrequency ablation (n=2) were used. Beta-blocker therapy was initiated in three patients presenting with severe arrhythmias in infancy, and in two of their asymptomatic siblings. Among the patients diagnosed in infancy (n=7), patients receiving beta-blockers (n=4) had a modestly longer PR interval (144±42 vs 135±24) and a significantly longer QRS duration (124±18 vs 81±18, p=0.03)
than those not receiving beta-blockers (n=3). A patient, event-free on beta-blockers for 12 years after severe arrhythmia in infancy, developed recurrent exercise-related arrhythmias (monomorphic VT, Figure 5) at the age of 13 years, requiring external cardioversion. He was receiving low dose (0.4 mg/kg/day) of propranolol at the time of the arrhythmia. The dosage of propranolol was gradually stepped up to 2.5 mg/kg/day and he also received an ICD. He had another episode of monomorphic VT at the age of 15 years in the early hours of the day and was externally cardioverted in the hospital. The sibling of this patient had presented with worsening conduction intervals

Table 1. SCN5A mutations in the study patients

<table>
<thead>
<tr>
<th>SCN5A Mutation</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Truncation mutations</strong></td>
<td></td>
</tr>
<tr>
<td>p.Trp156X</td>
<td>2</td>
</tr>
<tr>
<td>p.Thr630Thr</td>
<td>1</td>
</tr>
<tr>
<td>c.704-1G&gt;C</td>
<td>1</td>
</tr>
<tr>
<td>c.934+1G&gt;A</td>
<td>2</td>
</tr>
<tr>
<td>1570InsG</td>
<td>1</td>
</tr>
<tr>
<td>p.Arg1623X</td>
<td>1</td>
</tr>
<tr>
<td>c.2184-2186delACT</td>
<td>1</td>
</tr>
<tr>
<td>c.2582-2583delTT</td>
<td>3</td>
</tr>
<tr>
<td>3840+1G&gt;A</td>
<td>2</td>
</tr>
<tr>
<td>4118delT</td>
<td>1</td>
</tr>
<tr>
<td>5280delG</td>
<td>2</td>
</tr>
<tr>
<td><strong>M-inactive mutations</strong></td>
<td></td>
</tr>
<tr>
<td>p.Asp356Asn</td>
<td>2</td>
</tr>
<tr>
<td>p.Arg367Cys</td>
<td>1</td>
</tr>
<tr>
<td>p.Gly752Arg</td>
<td>2</td>
</tr>
<tr>
<td>p.Gly1743Glu</td>
<td>6</td>
</tr>
<tr>
<td><strong>M-active mutations</strong></td>
<td></td>
</tr>
<tr>
<td>p.Arg225Trp</td>
<td>2</td>
</tr>
<tr>
<td>p.Gly514Cys</td>
<td>2</td>
</tr>
<tr>
<td>p.Gly1319Val</td>
<td>2</td>
</tr>
<tr>
<td><strong>Missense mutations (unknown functional effect)</strong></td>
<td></td>
</tr>
<tr>
<td>p.Asp1243Asn</td>
<td>2*</td>
</tr>
<tr>
<td>p.Met1335Arg</td>
<td>2*</td>
</tr>
<tr>
<td>p.Asp1741Tyr</td>
<td>1</td>
</tr>
<tr>
<td>p.Phe1293Ser*</td>
<td>1</td>
</tr>
</tbody>
</table>

* These patients had an M-inactive mutation as well; * Polymorphism
Figure 4. Twelve-lead ECG at baseline (A) and during fever (B) in an asymptomatic 7-year old girl with loss-of-function SCN5A mutation. Note the fever-induced prolongation of conduction intervals and increase in ST-segment elevation in V2 and V3 (arrows). ECG calibration: 25 mm/second, 10 mm/mV.

Figure 5. Twelve-lead ECG in a 13-year old boy with compound heterozygosity. Baseline ECG (A) shows severely prolonged conduction intervals (PR interval 238 ms, QRS duration 184 ms). He had recurrent sports-related monomorphic VT (B) requiring external cardioversion. ECG calibration: 25 mm/second, 10 mm/mV.
in infancy and had hemodynamically unstable 2:1 atrioventricular block at the age of one year in 1994, for which she received isoproterenol. She however succumbed to intractable ventricular arrhythmias which ensued. 9 Another patient, presenting with fever-related ACA at age 4 months and subsequently treated with beta-blockers had episodes of monomorphic VT during fever at ages 5 months and 1.5 years, respectively. Both episodes occurred while being monitored for fever in hospital and were managed with aggressive antipyretics; intravenous esmolol was successfully given during the latter episode. Beta-blocker treatment at a high dosage (6 mg/kg/day metoprolol) was continued in this patient and ICD treatment was consciously withheld due to tachycardia-related ventricular arrhythmias.

Figure 6 depicts the occurrence of cardiac events in relation to age of patients (n=16). While cardiac events are observed to occur at all ages in affected children, it is interesting that most (80%) of the life-threatening events occurred in infancy.

**Event Triggers**

Eight fever-associated events occurred in six study patients, and two of these were vaccination-related fever episodes. Fever-triggered events were ACA, monomorphic
VT, atrial flutter, syncope and worsening of ECG abnormalities. SCD had occurred in a male infant in temporal relationship to vaccination. Physical activity-related arrhythmias were documented in one patient during adolescence.

Discussion
This study describes the clinical spectrum of loss-of-function cardiac sodium channelopathies in the pediatric population. As reported earlier in infants and very young children, prolonged cardiac conduction intervals have emerged as the most common manifestation of disease in this age-group and accompany both atrial and ventricular arrhythmias. In contrast, Type 1 BrS ECG was present in a much smaller proportion of patients in this study. This could be explained by the fact that right precordial ST elevation comprises just one aspect of this disease spectrum and also by the recognition that the pathophysiology of BrS includes various elements beyond mutant sodium channels. The gender propensity of BrS evidenced in our cohort has been described earlier and has been reported to be linked to a severe disease in men.

Fever has been identified as a trigger for arrhythmic events in children and adults with BrS. In the present study, fever-related symptoms occurred not only in patients with BrS phenotype but also in patients with cardiac conduction disease and atrial arrhythmias. Moreover, worsening of ECG abnormalities was evidenced during fever episodes in previously asymptomatic patients harboring a channelopathy. Vaccination-related fever was associated with cardiac events in three patients in this study; interestingly, an infant had succumbed to refractory ventricular arrhythmias on the day following vaccination. The management implications of these associations are twofold: firstly, parents have to be counselled on the importance of antipyretic measures during fever and on the need for prophylactic antipyretic medication during and immediately after vaccination; and secondly, ECG monitoring is essential during fever episodes and, probably, at the time of vaccinations to enable timely detection and treatment of arrhythmias. It is also imperative that the family and primary care physicians are provided with a list of drugs to be avoided.

Long-term management of symptomatic patients comprises of pharmacological treatment, device therapy, or a combination of both. The role of beta-blockers in treating patients with loss-of-function sodium channelopathies warrants discussion. Conventionally speaking, BrS is recognized as a bradycardia-related arrhythmic disorder in which the role of beta-blockers seems counter-intuitive indeed. However, it is imperative to note that in the pediatric population, particularly in infants and young children, the clinical picture is dominated by tachycardia-induced conduction disturbances, exemplified by the fever-related arrhythmias in this cohort. It is in these patients that beta-blockers, with their inherent ability to control heart rate have proven useful, as evident from the dramatic acute response of life-threatening arrhythmias to beta-blockers in two of the infants in this study and the long term effect in these two and three other patients. Both the infants with the acute favourable...
response had manifested with progressive widening of QRS complex accompanied by hemodynamic instability during atrial pacing with increasing cycle length, provoking the decision to treat with beta-blockers. Moreover, history of isoproterenol-related worsening of arrhythmias and SCD in the sibling of one of the infants leads us to believe the potentially impressive role of beta-blockers in such situations. It is clear from the present study that infants treated with beta-blockers had a severe phenotype with more conduction delay at baseline than the infants who did not receive beta-blockers, proving the beneficial effect of beta-blockers in the severely affected infants with tachycardia-related events.

ICD, which undoubtedly has a role in the management of high-risk cases, should be used with caution in young patients for the following reasons: due to the inherent risk of inappropriate shocks in young children, and more importantly, due to the potential risk of a vicious cycle of sinus tachycardia leading to inappropriate shocks which in turn could worsen the tachycardia finally culminating in fatal ventricular arrhythmias. The threshold for ICD therapy differed among the participating centres; however, as only one patient had an event after ICD implantation, it would be prudent to resort to device therapy only in the high-risk patients in whom medical management is unlikely to provide adequate arrhythmia-protection. As none of the patients in this study were treated with quinidine (due to unavailability), we are unable to comment on the usefulness of this drug which has been reported to be effective in managing BrS patients.2,15

While family-history, symptomatology and ECG are known to play a significant role in identifying at-risk individuals, genetic testing seems to have not only a diagnostic but also a prognostic role in these young patients. Clinical data on eight patients (belonging to four families) has been reported earlier;2,9,14,16 however, the present study comprises a unique cohort of pediatric cases with genetically confirmed loss-of-function sodium channelopathies presenting with a wide phenotypic spectrum. We have previously reported on the correlation between type of SCN5A mutation and clinical severity and conduction-slowing in patients with loss-of-function sodium channelopathies,8 and on the severe symptoms associated with compound heterozygosity in one family.9 Data from the present study is in concurrence with these findings. The small size of the study group is a limiting factor but it has to be highlighted that these are undoubtedly rare conditions in children and that diagnosing them is a challenge due to the highly heterogeneous nature of the disease.

Conclusions
Loss-of-function cardiac sodium channelopathies are a potentially lethal group of disorders in children, with fever and vaccination acting as arrhythmia-triggers. Prolonged cardiac conduction intervals on the electrocardiogram may be clues to diagnosis in this patient population. Treatment strategies include aggressive antipyretic measures, hospitalisation and monitoring during fever, beta-blocker therapy in young patients with tachycardia-related arrhythmias, and ICD for the high-risk cases.
References


