

## Loss-of-Function Sodium Channel Mutations in Infancy A Pattern Unfolds

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The role of channelopathies in the pathogenesis of sudden cardiac death in patients with structurally normal hearts is a rapidly evolving story.<sup>1</sup> Many ion channels are involved, including loss-of-function sodium channelopathies, of which the phenotypic spectrum ranges from lethal arrhythmias to asymptomatic carriers and includes Brugada syndrome (BrS), cardiac conduction disease, sick sinus syndrome, atrial fibrillation, and dilated cardiomyopathy. BrS, characterized by right precordial ST elevation on the ECG, is frequently associated with conduction delay, potentially lethal arrhythmias, and a positive family history of sudden premature death. BrS is estimated to be responsible for ≈4% of all sudden deaths and 20% of sudden deaths in patients with structurally normal hearts. Despite an overall prevalence of ≈5/10 000 individuals,<sup>2</sup> BrS is considered extremely rare in the pediatric population. However, children harboring loss-of-function mutations in the gene coding for the sodium channel  $\alpha$ -subunit (*SCN5A*) have been reported to present with life-threatening arrhythmias, especially during febrile episodes.<sup>3</sup> While *SCN5A* mutations account for 11% to 28% of BrS probands, mutations of the L-type calcium channel, including the gene coding for the L-type calcium channel  $\beta$ -subunit (*CaCNB2*), among others, have recently been implicated in ≈13% of patients with BrS-related phenotypes and sudden cardiac death.<sup>4</sup>

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In this issue of *Circulation*, Kanter et al<sup>5</sup> describe their experience with very young children manifesting ventricular arrhythmias due to previously undetected loss-of-function sodium and/or calcium channelopathies. Twenty of 32 patients <2 years of age with rapid ventricular tachycardia (VT) or ventricular fibrillation (VF), had known structural heart disease, and 9 of the remaining 12 patients had intraventricular conduction delay (IVCD) or Brugada pattern (coved) ECG, of which 4 had associated conditions (myocarditis, Barth syndrome, and drug use). The clinical features and subsequent management and follow-up of the remaining 5 patients are reported in detail. Interestingly, all 5 patients had at least 1 disease-causing mutation in *SCN5A* or *CaCNB2*.<sup>5</sup>

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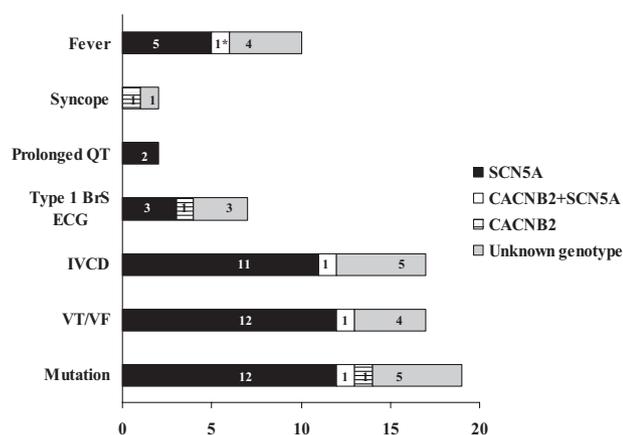
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This is the first single-center observational study of the manifestations of these channelopathies in such a young patient population and provides some valuable insights into the phenotypic and genotypic nature of the disorder. However, in the past decade, an increasing number of children <2 years of age have been reported with similar clinical characteristics.<sup>3,5-16</sup> The striking features of these 19 (including the Kanter et al series) previously healthy infants are as follows: (1) VT/VF was the presenting feature in 89% of patients (rapid VT at presentation was a selection criterion of Kanter et al, and occurrence of VT/VF could have also led to a reporting bias of the other cases reported in the literature); (2) IVCD was present in 89% of patients; (3) type 1 BrS ECG was present in 37% of patients of which 71% were spontaneous; and (4) fever-related arrhythmias occurred in 53% of patients (Figure). Of the 13 patients with *SCN5A* mutations, all but one (92%) presented with IVCD, whereas only 2 (15%) patients had a spontaneous type 1 BrS ECG (see also Figure 4 in the article by Kanter et al) and 1 patient showed the type 1 BrS ECG after drug challenge. It is noteworthy that 2 of these 13 patients had VT and IVCD at 5 months of age, within 1 to 2 days of receiving their standard childhood immunization, with documented fever in one of them.<sup>5,6</sup> *SCN5A* mutations were of nonsense/frameshift type in 7 patients (including 3 compound heterozygotes), missense (*D356N*) with complete loss of sodium current in 1 patient, missense (*I230T*) with significant loss of sodium current in 1 patient (homozygosity of patient and 3 siblings), missense (*Q270K*) with both loss- and gain-of-function properties in 1 patient, and missense mutation (*R1193Q/L567Q*) with marked acceleration of sodium channel inactivation in 2 patients. An *SCN5A* mutation (*IVS10+2 t>a*) of unknown functional significance was reported in a patient harboring 2 L-type calcium channel mutations.

In this unique patient population of children <2 years of age, IVCD manifesting as wide QRS complex monomorphic tachycardia appears to be the most dominant sign of disease as opposed to what is observed in adults. Although the exact mechanism behind this is unclear, it is obvious that these young patients with loss-of-function sodium channelopathies possess arrhythmogenic substrates that make them easy prey for potentially lethal ventricular arrhythmias, especially in the setting of fever, a common feature in infancy. There is also substantial evidence to believe that individuals carrying an *SCN5A* mutation with severe loss-of-function properties such as frameshift mutations “or double hits,” like most of these children, develop a more severe phenotype with an arrhythmogenic substrate facilitating monomorphic VT, in comparison with mutation carriers with just channel dysfunction.<sup>17</sup>



**Figure.** Characteristics of loss-of-function sodium and calcium channelopathies from published reports of 19 symptomatic children <2 years of age. \* This patient had no fever at presentation but had an appropriate ICD discharge during an episode of fever. BrS indicates Brugada syndrome; IVCD, intraventricular conduction delay; VF, ventricular fibrillation; VT, ventricular tachycardia.

Four patients that did not survive the initial arrhythmia had *SCN5A* mutations (including 2 compound heterozygotes). One patient presenting with fever-related syncope and atrial flutter with spontaneous type 1 BrS ECG (not genotyped) died suddenly during follow-up while reportedly not receiving treatment. Among the patients ( $n=14$ ) that survived, management involved pharmacological therapy alone in 43% of patients, pharmacological therapy and implantable cardioverter defibrillator (ICD) in 29%, pharmacological therapy and pacemaker in 7%, and no treatment in 21% of patients. The male preponderance seen in adults was absent; 58% of reported infants were female.

Of the 5 patients studied by Kanter et al,<sup>5</sup> 1 patient was treated with quinidine alone (rapid response of VF to quinidine, withdrawn by parents after 3 months of treatment), 1 was treated with quinidine and ICD (quinidine discontinued later because of extreme QRS prolongation), 2 patients were treated with propranolol and ICD (one of them also received mexiletine), and 1 patient (presenting with syncope and BrS ECG) did not receive any treatment. During follow-up, an appropriate ICD shock was documented in 2 patients; one was identified during routine telemetry 5 months after a discharge at midnight in a patient who was initially treated with quinidine (and later discontinued), and the other occurred during fever related to otitis media in a patient receiving propranolol and mexiletine. ICD coil fracture, lead fracture, and inappropriate ICD discharges were documented in 1 patient. Kanter et al<sup>5</sup> have derived a comprehensive management schema for infants presenting with rapid VT and IVCD in whom other known causes of arrhythmia have been ruled out. The proposed pharmacological management of these patients includes  $\beta$ -blockers, quinidine, or lidocaine, based on the response of the individual patient's arrhythmia. Once stabilized, they suggest ICD therapy in patients of adequate size, together with aggressive antipyretic measures during febrile episodes and before immunization. Although we are in general agreement and commend the authors on their proposal, it should be highlighted that patient size may

not be the only critical factor in the decision to place an ICD in these patients. Not only are tachycardia-induced conduction abnormalities very common in these young children, but rapid supraventricular tachycardia with conduction delay could also closely mimic VT. Indeed, ICD therapy, being associated with an inherent risk of inappropriate shocks in very young patients with fast supraventricular arrhythmias mimicking VT and with other mechanical complications, may prove dangerous. These inappropriate shocks might be followed by sinus tachycardia, which, in the setting of use-dependent characteristics of a loss-of-function sodium channel disorder, could easily deteriorate into a (potentially lethal) wide QRS complex arrhythmia.  $\beta$ -blockers, generally counterintuitive as a choice of therapy in these wide QRS-complex ventricular arrhythmias, may indeed prevent (sinus-)tachycardia and thereby avoid worsening of the rate-dependent conduction disorder and associated arrhythmias in these young patients. Several successful examples have been reported.<sup>5,6,9,12,13,16</sup>

Quinidine, on the other hand, is known to suppress the induction of ventricular arrhythmias in BrS by its ability to inhibit the transient outward current ( $I_{to}$ ) and by its anticholinergic effect, and it seems to be effective in children.<sup>3,18</sup> Although the class 1A antiarrhythmic effect of quinidine is apparently not detrimental in patients with BrS, caution is warranted, especially in very young patients with drastic loss of sodium channel function, as evidenced in a case reported by Kanter et al,<sup>5</sup> where quinidine had to be discontinued because of extreme QRS widening. It should also be emphasized that the long-term adverse effects of quinidine in children are currently unknown. Only rarely reported effective in BrS, there is no convincing evidence for lidocaine to feature in the management schema. Intuitively, even an inactivated state sodium channel block with a fast dissociation time constant could be detrimental. At this point, a treatment strategy combining pharmacological therapy ( $\beta$ -blockers, eventually quinidine, both with close monitoring of conduction intervals at different heart rates) with prudent antipyretic measures, in-hospital monitoring during immunization and febrile episodes, and adequate parent counseling might be an appropriate alternative to ICD in many of these infants.<sup>6</sup>

In the causation of sudden infant death syndrome (SIDS), mutations of the sodium channel-related genes seem the most malignant, accounting for 10% of SIDS cases.<sup>19</sup> Interestingly, death as an adverse event following immunization, even though it is uncommon, ranged from 1.4% to 2.3% of all adverse events following immunization reported between 1991 and 2001, and most of these deaths were classified as SIDS.<sup>20</sup> The recent presentation of a 4-month-old girl with aborted cardiac arrest and recurrent ventricular arrhythmias associated with vaccination and/or fever in this infant and in her brother,<sup>6</sup> the occurrence of SIDS in a 3-month-old boy on the day after vaccination (unpublished data), and the study by Kanter et al<sup>5</sup> reporting rapid VT in a 5-month-old boy on the day of vaccination, all cases united by an underlying loss-of-function *SCN5A* mutation, lead us to believe that there might be more to sudden deaths following immunization than just SIDS. With population-based studies on SIDS cases revealing

imperative information on molecular and genetic pathology of death in many of these infants, careful scrutiny for documented temporal relationship to immunization should be performed to verify this association. With genetic confirmation of the causal mutations in the SIDS/aborted sudden cardiac death patients, family screening should be a mandatory part of the management of these patients. Identification of asymptomatic mutation carriers and/or different phenotypic presentations among other young children in the family will help initiate targeted therapy aimed at arrhythmia prevention.

In summary, loss-of-function sodium and calcium channelopathies may present as sudden death in infants and young children, especially in association with febrile episodes and immunization. Pharmacological therapy together with adequate parental counseling should suffice in most patients, and ICD therapy should be reserved for the refractory cases.

### Disclosures

Dr Wilde is a member of the scientific advisory boards of Transgenomics and Sorin.

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