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

Running title: Chockalingam et al.; Brugada-like syndrome in infancy

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Key words: editorial; Brugada syndrome; genetics; ion channels or ion channel; sudden death; ventricular arrhythmia
The role of channelopathies in the pathogenesis of sudden cardiac death (SCD) in patients with structurally normal hearts is a rapidly evolving story.\(^1\) 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 electrocardiogram, 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 approximately 4% of all sudden deaths and 20% of sudden deaths in patients with structurally normal hearts. Despite an overall prevalence of about 5/10000 individuals,\(^2\) 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.\(^3\) While SCN5A mutations account for 11-28% of BrS probands, mutations of the L-type calcium channel (LTCC), including the gene coding for the LTCC beta-subunit (CaCNB2) among others, have recently been implicated in about 13% of patients with BrS-related phenotypes and SCD.\(^4\)

In this issue of Circulation, Kanter et al describe their experience with very young children manifesting with ventricular arrhythmias due to previously undetected loss-of-function sodium and/or calcium channelopathies.\(^5\) Out of 32 patients < 2 years of age and with rapid ventricular tachycardia (VT) or ventricular fibrillation (VF), 20 had known structural heart disease, and 9 of the remaining 12 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 one disease-causing mutation in SCN5A or CaCNB2.\textsuperscript{5}

This is the first single-centre 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.\textsuperscript{3, 5-16} The striking features of these 19 (including Kanter et al series) previously healthy infants are (1) VT/VF being 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 literature), (2) presence of IVCD in 89% of patients, (3) presence of type 1 BrS ECG in 37% of patients of which 71% were spontaneous and (4) occurrence of fever-related arrhythmias in 53% of patients (Figure 1). Of the 13 patients with SCN5A mutations, all but one (92%) presented with IVCD while 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 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.\textsuperscript{5, 6} SCN5A mutations were of nonsense/frameshift type in 7 patients (including 3 compound heterozygotes), missense (D356N) with complete loss of sodium current in 1, missense (I230T) with significant loss of sodium current in 1 (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 \textgt; a) of unknown functional significance was reported in a patient harboring two LTCC 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. While 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, compared with mutation-carriers with just channel dysfunction.17

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 cases (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,5 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 due to extreme QRS prolongation), 2 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 five 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 one patient. Kanter et al 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 stabilised, they suggest ICD therapy in patients of adequate size, together with aggressive antipyretic measures during febrile episodes and prior to immunization. While 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 also rapid supraventricular tachycardia with conduction delay could closely mimic VT. Indeed, ICD therapy, being associated with an inherent risk of inappropriate shocks in very young patients with fast supra ventricular 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 counter-intuitive 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. 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 (Ito) and by its anticholinergic effect and seems to be effective in children. While 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 where quinidine had to be discontinued due to 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 counselling might be an appropriate alternative to ICD in many of these infants.

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. Interestingly, death as an adverse event following immunization (AEFI), though uncommon, ranged from 1.4-2.3% of all AEFI reported between 1991 and 2001 and the majority of these deaths was classified as SIDS. The recent presentation of a 4 month old female with aborted cardiac arrest and recurrent ventricular arrhythmias associated with immunization and/or fever in this
infant and in her brother\(^6\), the occurrence of SIDS in a 3 month old male on the day after immunization (unpublished data), and the study by Kanter et al reporting rapid VT in a 5 month old male on the day of immunization\(^5\), 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 carried out to verify this association. With genetic confirmation of the causal mutations in the SIDS/aborted SCD victims, 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 counselling should suffice in most patients and ICD therapy should be reserved for the refractory cases.

**Conflict of Interest Disclosures:** Dr. Wilde is a member of the scientific advisory board of Transgenomics and Sorin.

**References:**


**Figure Legend:**

**Figure 1.** 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=Brugada syndrome, ECG=electrocardiogram, IVCD=intraventricular conduction delay, VF=ventricular fibrillation, VT=ventricular tachycardia
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Circulation, published online November 16, 2011;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/early/2011/11/16/CIRCULATIONAHA.111.071837

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