The role of channelopathies in the pathogenesis of sudden cardiac death in patients with structurally normal hearts is a rapidly evolving story. 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 $\approx 4\%$ of all sudden deaths and $20\%$ of sudden deaths in patients with structurally normal hearts. Despite an overall prevalence of $\approx 5 / 10000$ individuals, 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 ($\text{SCN5A}$) have been reported to present with life-threatening arrhythmias, especially during febrile episodes. While $\text{SCN5A}$ 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 ($\text{CaCNB2}$), among others, have recently been implicated in $\approx 13\%$ of patients with BrS-related phenotypes and sudden cardiac death.$^4$

In this issue of *Circulation*, Kanter et al$^5$ 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), 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 $\text{SCN5A}$ or $\text{CaCNB2}$.5

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.$^3,5–16$ 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 $\text{SCN5A}$ mutations, all but one (92%) presented with IVCD, whereas only 2 (15%) 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.$^3,6$ $\text{SCN5A}$ 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 $\text{SCN5A}$ mutation ($IVS10+2 \rightarrow \alpha$) 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 $\text{SCN5A}$ 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.$^{17}$

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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**Editorial**

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

Priya Chockalingam, MBBS; Arthur A.M. Wilde, MD, PhD
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 receiv-
ing treatment. Among the patients (n=14) that survived, 
management involved pharmacological therapy alone in 43% 
of patients, pharmacological therapy and implantable cardio-
verter 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 
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 conduc-
tion 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 (poten-
tially lethal) wide QRS complex arrhythmia. β-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.5,6,9,12,13,16

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 (Ip), and by its anticho-
linergic effect, and it seems to be effective in children.3,18 
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,5 where quinidine had to be discontinued 
because of extreme QRS widening. It should also be empha-
sized 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 dissocia-
tion time constant could be detrimental. At this point, a 
treatment strategy combining pharmacological therapy (β-
blockers, eventually quinidine, both with close monitoring of 
conduction intervals at different heart rates) with prudent 
antipyretic measures, in-hospital monitoring during immuni-

cation and febrile episodes, and adequate parent counseling 
might be an appropriate alternative to ICD in many of these 
infants.6
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.19 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.20 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,6 the occurrence of SIDS in a 3-month-old boy on 
the day after vaccination (unpublished data), and the study by 
Kanter et al5 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

**Figure.** Characteristics of loss-of-function sodium and calcium channelopathies from published reports of 19 symptomatic chil-
dren <2 years of age.7 This patient had no fever at presenta-
tion 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.

<table>
<thead>
<tr>
<th>Fever</th>
<th>Syncope</th>
<th>Prolonged QT</th>
<th>Type 1 BrS ECG</th>
<th>IVCD</th>
<th>VT/VF</th>
<th>Mutation</th>
</tr>
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<tbody>
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<td>5</td>
<td>4</td>
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Legend: SCN5A, CACNB2+SCN5A, CACNB2, Unknown genotype.
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.

References

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