Sodium Current Disorders
Clinician's View

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KEYWORDS

• Sodium current disorder • Brugada syndrome • Long QT syndrome • Sick sinus syndrome
• Cardiac conduction disturbance • Atrial fibrillation • Dilated cardiomyopathy

KEY POINTS

- The mechanism of sodium current disorders remains largely unknown and carriership of a mutation in one of the sodium channel–related genes has as yet no relevance for clinical decision making except for long QT syndrome type 3 (LQT3).
- Research has shown the complexity of sodium current disorders but has also implicated the involvement of common/rare gene variants or newly found sodium channel interacting proteins.
- Research findings have given possibilities for untangling the intricate mechanism of sodium current disorders.
- Further genetic and functional research on sodium current disorders may provide clinically relevant insights into sodium current disorders in the future.

INTRODUCTION

The complexity of sodium current disorders was presented in several reports in the late 1990s. One article published in 1999 reported on a large Dutch family carrying a single familial mutation, *SCN5A* 1795insD. This mutation shows gain- and loss-of-function of sodium channel and leads to overlap syndrome manifesting several different phenotypes, such as Brugada syndrome (BrS), long QT syndrome (LQTS) type 3 (LQT3), and cardiac conduction disease (CCD).[1] With regard to structural disease, an *SCN5A* mutation was reported in 1996 in a family with dilated cardiomyopathy (DCM) and bradyarrhythmias and/or tachyarrhythmias.[2]

Extensive research has been performed to date to unravel the complexity of sodium current disorders (including overlap syndrome), which resulted in elucidation of part of their mechanisms. Yet, this new knowledge has brought us to an even more intricate world. For example, clinicians have come to realize that the sodium channel forms a macro molecular complex including sodium channel α- and β-subunits and interacting proteins. This is an exciting discovery, considering that genetic analysis encoding such proteins and their functional tests may provide further insight into sodium current disorders and may eventually lead to better risk stratification or treatments. As another exciting aspect, the advance of genotyping technology brought the possibility of sequencing the whole genome to find variants associated with a disease. This will certainly bring more clues of primary electrical disease, such as sodium current disorders. However, it means that many more steps in research are required before clinicians fully understand the whole picture of sodium current disorders.

Currently, much remains unknown with respect to the (patho)physiology of sodium current disorders, and mutation carriership in the sodium channel–related genes and related proteins

Disclosures: The authors have nothing to disclose.
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Card Electrophysiol Clin 6 (2014) 819–824
http://dx.doi.org/10.1016/j.ccep.2014.08.003
1877-9182/14/$ – see front matter

unfortunately does not help clinicians to sort out patients at risk of arrhythmia in most instances. This article provides the clinicians' view on sodium current disorders.

SODIUM CURRENT DISORDERS: MISSING LINK FROM BENCH TO BEDSIDE

"Cardiac sodium current disorder" seems a simple nomenclature, but it includes diverse diseases, such as BrS, congenital LQTS, sick sinus syndrome (SSS), CCD, atrial fibrillation (AF), and DCM. Although these diseases commonly harbor a mutation in genes encoding an α- or β-subunit of the cardiac sodium channel, clinical manifestations vary among these diseases, and the mechanisms leading to different clinical phenotypes are poorly understood. The complexity of sodium current disorders is even evident within a single sodium current disease. For example, although BrS is considered to follow a mendelian autosomal-dominant inheritance pattern, studies in BrS families carrying a familial *SCN5A* mutation have repeatedly shown incomplete penetrance with variable expressivity. Thus, family members carrying the familial *SCN5A* mutation do not always manifest the same clinical features and may show different phenotypes, such as ventricular fibrillation (VF), cardiac conduction abnormality, or no symptom for life.[1,3] Such a phenomenon also has been reported in LQTS and DCM.[2,4] Another aspect of sodium current disorders is that, whereas conduction abnormality and the involvement of sodium channel–related genes are naturally expected to be involved in the pathogenesis of SSS, CCD, AF, or DCM, mutations in sodium channel–related genes are rarely found.[5–8] Because of an incomplete understanding of the mechanisms underlying sodium channel (dys) function, and of the ways in which it may be causal to the disease,[9,10] mutation carriership itself is currently of not much help in clinical practice, except for LQT3, in which genotype confirmation plays an important role in the choice of treatment.

Recent extensive clinical and experimental research has implicated that sodium current disorders may be not monogenic but may be more complex than previously expected.[10–14] For example, age and gender are well known modifiers of sodium current disorders,[9] but common gene variants have been additionally suggested to be involved in modifying the disease status.[11,13,15] Furthermore, the sodium channel has been revealed to be part of a macromolecular complex, and several interacting proteins are implicated in sodium channel function.[12,16] This suggests that genes encoding such proteins may be new candidates for mutation screening and subsequent functional testing.

At present, comprehension of the mechanisms underlying sodium current disorders is still largely dependent on bench work, and further research is mandatory before new diagnostic tools or therapy for patients with a sodium current disorder can be introduced.

BRUGADA SYNDROME

From the clinicians' view, the most groundbreaking recent report on BrS is the successful elimination of recurrent VF episodes by epicardial ablation in the right ventricular outflow tract.[17] Abolishment of fragmented electrograms by ablation and the absence of VF recurrence during follow-up (except for one patient) strongly suggest the involvement of conduction abnormality in the pathogenesis of BrS. In that sense, it is natural to consider that genes encoding α- and β-subunits of the sodium channel or sodium channel interacting proteins (*SCN5A*, *SCN1B*, *SCN2B*, *SCN3B*, *GPD1L*, *RANGRF* [MOG1]) are involved in the pathogenesis of BrS. Carrying a mutation in one of such (putative) disease-causing genes is, however, not relevant for clinical decision making. As a matter of fact, mutations in SCN5A are found only in 20% of patients with BrS.[18] Mutations in *SCN5A* are most likely to be found in patients with BrS with long PR and QRS intervals on the electrocardiogram. Other genes have been found only in a few sporadic cases, except for *GPD1L*.[19] Clinical studies using a large cohort of patients with BrS have failed to show *SCN5A* mutation as a risk marker for future arrhythmic events.[20,21] Another point to keep in mind is that, in healthy subjects, a 2% to 5% background rate of rare variants was reported,[18] which implies that not all mutations found in BrS are causal for the disease. A recent clinical study by our group has raised additional doubts regarding the causality of *SCN5A* mutations in BrS.[10] In this study, we included 13 BrS families with more than five clinically affected individuals. In five families, one or two clinically affected individuals without the familial *SCN5A* mutation were observed,[10] suggesting that *SCN5A* mutations do not directly determine the BrS phenotype.[10] More recent genetic studies have implicated the involvement of common variants in the *SCN5A* promoter region or common variants in several genes (*SCN5A*, *SCN10A*, *HEY2*) in BrS.[11,15] At present, all patients with BrS, regardless of genotype or symptoms, are advised to avoid the use of sodium channel–inhibiting agents, as mentioned in the article by Postema and Woosley elsewhere in this issue. In addition, patients are to take measures