Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population
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Chapter 6

Fever induced Life-Threatening Arrhythmias in Children Harboring an SCN5A Mutation

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Abstract

Cardiac channelopathies due to \textit{SCN5A} mutations are well tolerated by most patients. However, the dramatic presentation of a previously healthy 4-month old female with life-threatening arrhythmias and the subsequent findings in the child and her family provide evidence that loss-of-function sodium channel mutations can present very early in life. An \textit{SCN5A} mutation was detected in the infant, her brother and their father. Both the siblings manifested with recurrent serious arrhythmias during febrile episodes that followed vaccinations as well as with fever of nonspecific origin. The management consisted of prompt antipyretic measures, hospitalization and vigorous monitoring during vaccination and febrile episodes, and prevention of tachycardia-induced conduction disturbance with \(\beta\)-blockers.
Introduction

The cardiac sodium channel encoded by the SCN5A gene is responsible for action potential initiation and propagation in excitable cells. Mutations of this gene can lead to either a loss-of-function or a gain-of-function of the sodium channel. The spectrum of phenotypes produced by loss-of-function sodium channelopathies ranges from lethal ventricular arrhythmias to asymptomatic carriers and includes Brugada Syndrome (BrS) and cardiac conduction defects. BrS, the most reported in this group of disorders, has been described typically in the adult population and occasionally also in children, fever being a well-appreciated arrhythmogenic trigger in affected patients. Recent evidence suggests that identifiable and potentially treatable cardiac channelopathies underlie approximately one third of autopsy-negative sudden unexplained deaths (SUD) in the young. Moreover, 70%-80% of SUD in infancy has no identifiable cause and is labelled as sudden infant death syndrome (SIDS). Fever, following vaccination or as a response to infection, is extremely common in infants and children and can lead to life-threatening arrhythmias in the setting of a cardiac sodium channel disorder, as reported here.

Patient Presentation

A previously healthy four-month old female suddenly became limp and cyanotic while being held by her grandmother at home. She was noted to have a wide-complex tachycardia with hemodynamic instability (Figure 1A) requiring defibrillation by the ambulance team. In the emergency room, she had a gasping respiration, bradycardia of 80 bpm and low blood pressure. She was intubated and given cardiopulmonary resuscitation. An electrocardiogram (ECG) showed a heart rate of 130 bpm, PR interval 112 ms, QRS duration 144 ms and QTc 400 ms. She was observed to be febrile (39.4°C). She apparently had flu-like symptoms since the day prior to the event. She had unremarkable prenatal and neonatal histories and had received her second dose of standard childhood immunization two weeks earlier. The two weeks following the vaccination had been uneventful.

In the following hours in intensive care, her course was complicated by frequent episodes of wide-complex tachycardia (Figure 1B), some necessitating external defibrillation. She was initiated on amiodarone in view of the recurrent arrhythmias. Subsequently, even during periods of sinus rhythm, short runs of polymorphic ventricular tachycardia (VT) persisted. Echocardiogram showed a structurally normal heart and coronary artery anatomy. Her oxygenation status failed to improve despite maximum ventilatory support combined with nitric oxide and her chest radiograph showed evidence of acute respiratory distress syndrome. She received extracorporeal membrane oxygenation (ECMO) for a period of 4 days. The metabolic acidosis noted on admission had normalised in a few hours and the serum electrolytes remained within normal limits. With viral blood cultures revealing Influenza A, the working diagnosis was viral myocarditis with the differential diagnoses being primary arrhythmia syndromes and metabolic disorders.
The child showed clinical improvement following ECMO. There were no further ventricular arrhythmias but frequent monomorphic ventricular extrasystoles (VES) persisted. Based on the suspicion of a primary arrhythmia syndrome and since there were no further signs to suggest viral myocarditis or metabolic disorders at this stage, β-blocker therapy (metoprolol 4 mg/kg/day) was initiated following which the VES subsided (Figure 1C). During the fourth week of hospitalisation the child was given her third dose of standard childhood immunization. The temperature on the day of vaccination was normal and her ECG parameters were within normal limits (Figure 2 left panel).

Figure 1. A Ambulance rhythm strip and B ECG on admission, both showing wide-complex tachycardia which could be supraventricular tachycardia with aberrant conduction or ventricular tachycardia (not very likely). C Arrhythmia subsided on β-blocker initiation, revealing significant conduction delay (PR 160ms, QRS 120ms) without ST elevation. D VT on re-admission with fever at 1.5 years. ECG calibration 25 mm/sec, 10 mm/mV.
However, she became febrile (38.6°C) a day later and her ECG showed tachycardia (170 bpm) with significant QRS widening with right bundle branch block (RBBB) morphology and left axis deviation (Figure 2 middle panel). With aggressive antipyretics and surface cooling, the body temperature reverted to normal in the next few hours and the arrhythmia characteristically returned to sinus rhythm with pre-existent conduction abnormalities (Figure 2 right panel). Incremental atrial pacing during electrophysiology study a few weeks later resulted in progressive widening of QRS complex with development of RBBB at a pacing rate of 150 bpm. Molecular analysis revealed a mutation in the 3p21 chromosome of the SCN5A gene (c.934+1G>A), a novel splice site mutation presumably causing protein splicing abnormalities of the cardiac sodium channel protein.

At discharge from hospital 2 months after the initial episode, the child was clinically stable. She received 6 mg/kg/d of metoprolol. After careful weighing of the advantages and disadvantages of placing an implantable cardioverter defibrillator (ICD), a decision to withhold ICD was made. However, a strict protocol of hospitalisation and monitoring during immunization and febrile episodes was instituted and the family was counselled on medications to avoid. She developed fever following two subsequent immunizations at ages 11 and 14 months but was free of arrhythmias. At the age of 1.5 years, when the child was admitted to intensive care with high fever (39.5°C), she again developed sustained VT (Figure 1D). The arrhythmia remitted with intravenous esmolol and aggressive antipyretic measures. She is currently 2.5 years old, has normal ventricular function on echocardiography and shows age-appropriate development.

Family Screening

The 3-year old male sibling had no complaints but the resting ECG showed evidence of conduction disturbance with broad QRS complex and coved-type ST segment elevation in leads V1 and V2 with a heart rate of 115 bpm and QRS duration of 120 ms (Figure 3). As he was also a carrier of the SCN5A mutation found in his sister, he was issued the same protocol of hospitalisation and monitoring during episodes of fever and immunization. During one such admission with fever and tonsillitis at the age of 4 years, he developed a non-sustained VT (visualised on the monitor, not documented) remaining hemodynamically stable. He was also treated with metoprolol and is well at 2 years of follow-up.

The children’s father, a 36-year old fitness instructor had remained asymptomatic but had ECG abnormalities suggestive of a conduction disorder (Figure 3) and was also found to harbor the same SCN5A mutation as his children. Based on the combination of findings in different family members the diagnosis BrS could be made, in this case associated with significant conduction defects. The mother was a healthy 33-year old woman with a normal ECG (Figure 3) and negative genotyping.

Discussion

The critical role played by fever, following vaccination or otherwise, in the causation of life-threatening arrhythmias in children with a sodium channelopathy, is clearly evident from this report. Cardiac channelopathies such as congenital long QT syndrome and
Figure 2. On the day of vaccination, ECG showed prolonged conduction parameters without right precordial ST elevation (left panel). A day later (38.6°C), ECG showed QRS widening, right bundle branch block, left axis deviation (middle panel). With temperature normalisation, ECG returned to sinus rhythm with pre-existent conduction abnormalities (right panel). ECG calibration 25 mm/sec, 10 mm/mV.
BrS have been implicated as potential causes of sudden death in children.\textsuperscript{3,4,6-9} The underlying mechanism causing rhythm disturbance is reduced sodium current which closely associates with BrS and (progressive) cardiac conduction disease.\textsuperscript{10} Children harbouring this genetic defect may present with SCD, syncope or supraventricular tachycardia (SVT) with fever being the most important trigger.\textsuperscript{10} There is also anecdotal evidence that these children may present with febrile seizures.\textsuperscript{11} The family reported here shows signs of BrS combined with pronounced conduction defects evident from the typical type 1 BrS ECG of the sibling while more of a conduction disturbance is present in the index patient. However, the tachycardia-induced delay in conduction is the most striking phenotype in both the children.

\textbf{Figure 3.} Pedigree shows members possessing loss-of-function SCN5A mutation (circle=woman, square=man, solid symbol=genetically affected family member, open symbol=unaffected member). Index patient and her father show ECG features suggestive of significant conduction disorder while sibling shows a characteristic type 1 Brugada Syndrome ECG (with significant conduction disease). ECG of mother is normal.
The role of fever as a precipitating factor for ventricular arrhythmias in subjects with sodium channel disorders is well recognized.\textsuperscript{3,12-14} While the exact mechanism remains unclear, one explanation is that mutations responsible for BrS alter the temperature sensitivity of fast inactivation of the sodium channel,\textsuperscript{15} while other studies show that the temperature-dependent properties of wild-type sodium channel itself might lead to the typical BrS ECG during fever.\textsuperscript{16} Recently, fever has also been implicated in prolonging the QT interval in LQT2 patients thereby leading to torsades de pointes and ventricular fibrillation.\textsuperscript{17}

Fever is one of the most common adverse effects of infant immunization.\textsuperscript{18,19} Fever as an adverse event following immunization (AEFI) is reported in 1\%-10\% of vaccinees but it can be as frequent as 30\%-70\% among vaccinees receiving multiple vaccines.\textsuperscript{20} Of the eight vaccinations received by the index patient and her sibling (including the novel H1N1 influenza vaccine and the vaccines in the Dutch childhood immunization schedule), four (50\%) vaccines were followed by fever. Four episodes of fever-related ventricular arrhythmias were documented in both siblings of which one was immediate post-vaccination and one two weeks after vaccination. Hence we would like to highlight that children harboring inherited cardiac channelopathies could present with potentially lethal arrhythmias triggered by fever of any origin including vaccination-related fever. This clinical picture should lead to a suspicion of an underlying cardiac ion-channel disorder which could be unraveled by a subsequent genetic analysis.

Careful surveillance during and after vaccination and prompt measures to abate fever are extremely important to prevent sudden death in these young patients. In addition to administration of adequate antipyretic therapy and ample surface cooling, hospitalization and monitoring of cardiac rhythm could save lives by aborting potentially fatal arrhythmias. Parents should also receive detailed instructions and advice about medications that could adversely affect these children (www.brugadadrugs.org).\textsuperscript{21} ICD is associated with the inherent risk of inappropriate shocks in very young patients with tachycardia-related ventricular arrhythmias. These 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 lethal arrhythmia. Indeed, β-blockers may prevent (sinus) tachycardia thereby preventing the worsening of the conduction disorder (and associated arrhythmias) with increased heart rate. Young patients could benefit from β-blocker therapy as evidenced in the siblings reported here. The role of quinidine (noted to be effective in some BrS patients) in this unique clinical setting of rate-dependent conduction delay needs to be studied.

Conclusions

Fever, either following immunization or of nonspecific origin, can lead to sudden death in infants and young children harbouring a loss-of-function sodium channel mutation. Abating fever with prompt antipyretic measures, hospitalization and vigorous monitoring during vaccinations and febrile episodes, and preventing tachycardia
using β-blockers could all play a major role in the prevention and management of life-threatening arrhythmias in affected patients.

References


