Identification of genetic abnormalities can aid in development of treatment plan for arrhythmia

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Our understanding of the genetic and cellular bases of arrhythmia among pediatric patients has grown exponentially in recent years. This field has enjoyed tremendous gains realized through synergies between bench scientists and astute observers in the clinical setting.

As new insights unfold, our paradigms are shifting in the way we describe, diagnose, monitor, treat and counsel many pediatric patients with diseases of heart rhythm and conduction.

The action potential, which generates a microcurrent propagated along the cardiac myocyte, results from the coordinated movement of ions across the cell membrane. The ions involved move through specialized channels in the membrane. Assuming an average heart rate of 100 beats per minute during the pediatric years, the heart beats nearly 1 billion times by age 18. Each pulse demonstrates the intricate interplay among proteins, ions and energy, which results in cardiac myocyte excitation and its mechanical coupling. When this complex and interactive system fails, one or more aspects of heart function may degrade.

Many genetic abnormalities involving the contractile elements of the sarcomere have been associated with the “mechanical” cardiomyopathies manifested by impaired myocyte contraction or relaxation. Now, genetic abnormalities impairing function of transmembrane ion channels and leading to disordered myocyte depolarization or repolarization are being recognized as forms of primary cardiomyopathy (Lehnart SE, et al. Circulation. 2007;116:2325-2345). As is the case for contractile myopathies, the phenotypic expression of arrhythmogenic myopathies is modified by genetic and environmental factors. As our understanding of these modifiers improves, our ability to quantify and mitigate risk will improve as well.

Several genetic abnormalities predispose children and adults to arrhythmias. Many result in altered function of ion channels, either by directly altering the channel itself or by altering proteins that modulate ion channel function. The voltage-gated sodium channel, several forms of potassium channels and proteins responsible for calcium cycling each have been implicated in abnormalities of myocyte excitation or repolarization.

Although the clinical expression of these genetic abnormalities may vary, several distinct genetically mediated arrhythmia syndromes have been characterized. These include the long QT syndromes, the Brugada syndromes, progressive cardiac conduction diseases, some forms of congenital heart block, sudden unexpected nocturnal death syndrome, some forms of sudden infant death syndrome (SIDS), familial atrial standstill, some forms of sick sinus syndrome, catecholaminergic polymorphic ventricular tachycardia, some forms of dilated cardiomyopathy and short QT syndrome.

Identification of genetic abnormalities can aid in development of treatment plan for arrhythmia

by Geoffrey L. Rosenthal, M.D., Ph.D., FAAP

Our understanding of the genetic and cellular bases of arrhythmia among pediatric patients has grown exponentially in recent years. This field has enjoyed tremendous gains realized through synergies between bench scientists and astute observers in the clinical setting. As new insights unfold, our paradigms are shifting in the way we describe, diagnose, monitor, treat and counsel many pediatric patients with diseases of heart rhythm and conduction.

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As molecular mechanisms become apparent, treatment strategies for inherited arrhythmogenic myopathies increasingly have become directed at the underlying electrophysiological perturbation. Those that are worsened by catecholamine stimulation may improve with beta-blockade. Those manifested by short QT may respond in some cases to class III anti-arrhythmics or quinidine (each of which tends to prolong QT). Those resulting from...
long QT benefit from avoidance of the myriad agents known to prolong QT (Sudden Arrhythmia Death Syndrome Foundation Web site, www.sads.org, provides reference materials regarding medications that prolong QT). And in some cases, implanted defibrillators are needed to control arrhythmias unresponsive to medical interventions or with high predicted lethality.

Since these clinical syndromes may result from different underlying genetic abnormalities, identification of specific genetic abnormalities often is needed to develop the most precise medical treatment plan. Commercially available genetic tests for several of the more prevalent forms of long QT syndrome may help direct specific therapy, as well as guide anticipatory care for relatives of index cases.

The importance of astute clinical skills, a careful past medical and family history, an electrocardiogram and a high index of suspicion in the diagnosis of arrhythmic cardiomyopathies cannot be overstated. Red flags should rise when any of the following points are elicited in the history and physical:

- sudden death (either SIDS or sudden unexpected nocturnal death);
- stress-induced syncope or seizures;
- drowning or single vehicle crashes;
- autism spectrum disorders or cognitive impairment;
- congenital deafness;
- dysmorphisms;
- muscular dystrophies;
- documented ECG abnormalities (bradycardia, conduction abnormality, abnormal T-wave morphology, repolarization abnormality); or
- documented arrhythmias (torsades de pointes, ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial standstill).

When questions about diagnosis, treatment and prognosis of inherited arrhythmogenic myopathies arise, pediatric electrophysiologists and geneticists are an invaluable resource.

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