HEREDITARY ARRHYTHMIA CORNER: LEARNING FROM CHALLENGING PATIENTS

Family with Suspect LQTS

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CASE #1—TWO YOUNG SIBLINGS WITH A FAMILY HISTORY OF LONG QT SYNDROME

A brother and sister, presented to our Arrhythmia Clinic for evaluation of possible long QT syndrome (LQTS). They are 18 and 15 years of age, respectively. Their mother has been diagnosed with LQTS and the family history is remarkable for a number of sudden deaths. The electrocardiogram (ECG) of the sister is presented in Figure 1.

The siblings had been followed by pediatric cardiology since infancy and now they are referred for further evaluation. They are both asymptomatic and very active teenagers, and are not on any medications. Echocardiograms were normal. Holter monitoring also did not show any rhythm abnormalities in either sibling.

The mother had been evaluated as a teenager when she had a presyncopal episode while running track in high school. Her QT interval on one 12-lead tracing showed borderline prolonged QT. She had originally been started on beta-blockers, but she had taken herself off of these over the years. The family history is significant for sudden deaths

in several distant relatives. In addition, the mother's aunt had an abnormal ECG (Fig. 2) in the setting of multiple syncopal episodes. In the interim, she had been treated with beta-blockers.

Dr. Viskin: What testing would you recommend next in the family?

Ruling out a long QT syndrome (LQTS) in asymptomatic individuals is far more difficult than deciding if a LQTS is present in symptomatic patients. This is because data from genotyped patients shows that a few carriers of LQT-mutations have QTc intervals as short as 360–380 milliseconds. Therefore, it is practically impossible to totally exclude the presence of LQTS. Consequently, instead of deciding if the asymptomatic family members "do not have LQTS," it will be easier to decide if the symptomatic family members have it. I would therefore focus on those who are most likely to be affected by the familial disease (if there is one). Specifically, before doing any tests on the youngsters I would review the ECG of any family member with history of cardiac arrest and then move to review all available ECGs of patients with syncope. Patients seeking to be screened (in this case the two youngsters) may become impatient with this type of recommendation and I generally explain that "it will be easier to decide if you have the disease if we know what

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Figure 1. Electrocardiogram of sister at presentation.

disease we are looking for." In this case, the mother and her own aunt are reported to have "recurrent syncope and borderline QT." I would review their clinical history to decide if the syncopal episodes suggest arrhythmic syncope and review as many ECGs as possible.

Too often, however, information on the truly affected family members is scant or absent. At the present time, I am given one ECG of the maternal aunt who has been diagnosed by others as "affected." Her trace (Fig. 2) shows sinus rhythm with mild sinus arrhythmia and normal P waves, PR and QRS intervals. There are obvious baseline move-

ment artifacts that are best seen after the T wave in many of the leads. Her QT appears to be around 450 and her corrected QT interval (QTc) around 440 milliseconds. For a female, this is the upper range of normal. I am uncertain about why others have diagnosed her as "LQTS" in the past, especially considering her normal T-wave morphology, but it may have been a misinterpretation of the baseline movement artifacts that are seen after the T wave.

Figure 1 belongs to the asymptomatic 15-year-old girl. She has inverted T waves in the right precordial leads; that is something to keep in mind if

Figure 2. Electrocardiogram of aunt.

the familial history of sudden death turns out to be more impressive than their QT interval. After all, other diagnoses (like right ventricular dysplasia) are possible. Her QTc is even less impressive (about 430 milliseconds).

The Holters are reported as showing "no arrhythmias." I would nevertheless carefully review the Holter traces to see if there is unusual QT prolongation during nocturnal bradycardia or following extrasystolic pauses. In addition, whenever there is a questionable diagnosis of "LQTS," a battery of tests may help clarify the diagnosis. Most centers use the exercise test and epinephrine challenge test because they have been rigorously tested in controlled settings. We find that the adenosine challenge test is very helpful because it shows how the QT behaves both during sudden bradycardia and during sudden tachycardia. Finally, we recently showed that simply asking the patient to stand up quickly and stay still allows for careful examination of the response of the QT interval to sudden heart rate acceleration.

The aunt underwent genetic testing that revealed negative results for any known mutations associated with long QT; however she tested positive for (RYR2 Lys4594 Thr) consistent with catecholaminergic polymorphic ventricular tachycardia (CPVT). Our patients' mother is currently noncompliant for genetic testing.

Dr. Viskin: Please make recommendations for the assessment of the patients' potential risks.

A genetic diagnosis should not be accepted as gospel but should be used to confirm the clinical diagnosis. Again, the correct approach is to first test those more likely to be affected (those with symptoms). Patients with CPVT have normal ECG at baseline (which matches what we have seen so far in this family) but usually have easily provokable arrhythmias with exercise. The most distinctive arrhythmia is "bidirectional VT." However, in a family with several cases of sudden death, reproducible provocation of any polymorphic VT during exercise would be accepted as diagnostic, especially if accompanied by exercise induced atrial arrhythmias. I would first review the exercise test of the genotyped aunt to reassure myself the diagnosis made somewhere else is correct and would then schedule our own asymptomatic patients for a maximal exercise test. The test should only be performed by physicians with expertise in this particular field of arrhythmias because potentially lethal arrhythmias may occur.

Treadmill testing in both siblings did not provoke any exercise related arrhythmias. The measured QTc intervals remained normal throughout exercise for both siblings. At peak heart rate the QTc calculated to be 401 milliseconds for the brother and 367 milliseconds for the sister.

Dr. Viskin: Please make recommendations for treatment and follow-up of the 2 patients.

The two patients have no clinical evidence of LQTS or CPVT. For all I know, they are healthy. They could still be asymptomatic carriers of CPVT if they have the mutation found in the maternal aunt. I would insist on reviewing the aunt's clinical data and exercise test to reassure myself that her identified mutation correlates with her phenotype. Only then I would perform a genetic in my two patients. Before they consent to genetic testing, it is important that our youngsters understand that a diagnosis of *asymptomatic CPVT mutation-carrier* could have profound implications for their real life (in terms of life-insurance policies and banning from competitive sports). On the other hand, I would emphasize that it is important to know if they are CPVT carriers because this is a highly malignant disease if left untreated for which beta-blocker therapy is very effective.

Since cardiac arrest may be the presenting symptom in CPVT carriers with negative exercise test, I would definitively recommend life-long beta-blocker therapy (at the maximal dosage that is well-tolerated) for any of the youngsters with positive genetic testing. Furthermore, since the risk for cardiac arrest despite beta-blocker therapy approaches 10% at 10 years in some series, I ask my patients to perform maximal exercise tests and Holter recordings twice yearly. I would add flecainide therapy if I ever see ventricular arrhythmias. I would not recommend implantable cardioverter defibrillator (ICD) implantation or left cardiac sympathetic denervation for asymptomatic CPVT but I encourage my patients to purchase an external automatic defibrillator (EAD) for home and to make sure an EAD exists wherever they exercise. I would emphasize the need for compliance with beta-blocker therapy and suggest they use automatic reminders; I would also highlight the importance of reporting any new symptoms and advice them to refer all the other family members for screening. I would conclude the discussion with our youngsters with an optimistic tone, emphasizing their healthy status at present and their good prognosis.