HEREDITARY ARRHYTHMIA CORNER: LEARNING FROM CHALLENGING CASES

A Young Patient with Exercise-Induced Polymorphic Ventricular Tachycardia

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CASE HISTORY—A YOUNG PATIENT WITH EXERCISE-INDUCED POLYMORPHIC VT

A 19-year-old female competitive runner presented to our clinic after a syncopal episode. She has a history of multiple episodes of syncope associated with blood draws. During this most recent event, she was running through a parking lot and had a syncopal episode in the midst of running. Her friends who witnessed the event saw her running into a parked car and hitting her head on the car's window. She regained consciousness shortly afterward with no residual symptoms and felt back to baseline quickly after the event. Socially she doesn't use any illicit drugs or herbal medications. She denies any family history of sudden cardiac death or known inherited arrhythmias. She was admitted to the hospital and underwent a cardiac evaluation. A Holter monitor demonstrated rare episodes of AV nodal Wenckebach and nonsustained irregular ventricular tachycardia. Echocardiogram revealed a preserved left ventricular function ejection fraction of 60% and a structurally

normal heart. Her electrocardiogram (ECG) upon presentation is shown in Figure 1.

Dr. Daubert: Please list what the differential diagnoses may be for this scenario and what testing would you recommend next

We are presented with a 19-year-old patient who experienced an episode of exertional syncope in the setting of normal left ventricular function (without evidence of LV hypertrophy) and runs of nonsustained ventricular tachycardia on a Holter monitor. I would initially try to rule out one of the several ion channel disorders that are associated with increased arrhythmic risk without structural heart disease. The presence of catecholaminergic polymorphic ventricular tachycardia (CPVT) is compatible with the present case due to the setting, and is therefore an important initial consideration in our patient. Long QT syndrome (LQTS) and Short QT syndrome are also possible; however, the ECG in Figure 1 shows no evidence of either prolongation or shortening of the duration of the corrected QT interval despite some abnormalities in the pattern of repolarization. It is important to remember that arrhythmic events can occur even in phenotype-negative carriers of LQTS mutations (i.e., without overt QTc prolongation), therefore the

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Figure 1. Twelve-lead electrocardiogram at presentation.

presence of LQTS cannot be ruled out without additional testing. Brugada syndrome should also be considered. There is no suggestion of a Brugada pattern in the presented ECG, although the pattern may be concealed and provokable by a sodium channel blocker or other measures.

Among arrhythmic disorders with structurally abnormal hearts, arrhythmogenic right ventricular dysplasia (ARVD), and hypertrophic cardiomyopathy (HCM) are important to consider. The presence of ARVD is suggested by the T-wave inversion in V_3 and flat T-waves in V_1 - V_2 . The normal echocardiogram in our patient cannot rule out ARVD since an echo may miss subtle RV dysfunction that is present in an important subset of patients with this disorder. Most HCM patients show ECG abnormalities, although the tracing provided in Figure 1 does not have classic signs of HCM. Similar to ARVD, an echocardiogram may miss a localized region of hypertrophy in some unusual cases of HCM. Thus, magnetic resonance imaging (MRI) may be helpful in detecting subtle abnormalities in both ARVD and HCM patients.

Finally, a neurocardiogenic mechanism may also be the cause of the recurrent syncopal events in our patient, although the history of exertional syncope makes this a treacherous diagnosis. Very atypical cases of neurocardiogenic syncope may occur with exertion, but I would consider this diagnosis with great trepidation, only after the above-conditions have been ruled out.

In summary, the main disorders that I would be considering in this patient are CPVT, LQTS, or

ARVD. To proceed with the diagnosis I would recommend obtaining the following tests: (1) exercise treadmill test (ETT), looking for arrhythmias being provoked; (2) Cardiac MRI, looking at right ventricular function, right and left ventricular scar, and hypertrophy; and (3) evaluation of family by history, exam, ECG, and possibly echocardiogram, to assess the possible existence of one of the above inherited cardiac arrhythmic disorders in a first-degree family member.

An exercise treadmill test was ordered and 2 of the representative tracings, first one during exercise and second one during early recovery, are presented in Figures 2A and B, respectively.

Dr. Daubert: Please comment on your thoughts on the tracings and what therapy would be recommended for this patient? Furthermore, she is now contemplating pregnancy. Will this be advisable and what will be the appropriate next steps to recommend?

The ETT shows frequent ventricular premature complexes (VPCs) with exercise and they have a variable morphology; there is a bidirectional pattern in one of the tracings which is quite suggestive of CPVT (but it can also be seen in digoxin toxicity). With consideration of CPVT as the primary diagnosis, I would recommend beta-blockers as a first-line therapy. Due to the presence of frequent polymorphic ventricular ectopy and nonsustained ventricular tachycardia during recovery, implantation of a cardioverter defibrillator (ICD) should also be considered if arrhythmias or syncope occur despite beta-blocker therapy. In addition, calcium

Figure 2. Electrocardiogram during exercise testing and recovery (A) Peak exercise. (B) Recovery.

channel blockers may be beneficial in some CPVT patients, and cardiac sympathectomy may also be considered in medically refractory cases.

Pregnancy and the postpartum period are characterized by physiologic and mental stress. Therefore, arrhythmias may be more common during these time-periods, although there is limited information

on the effect of pregnancy in arrhythmic risk in patients with CPVT. One case report found frequent ventricular arrhythmias from CPVT producing reversible LV dysfunction during pregnancy requiring flecainide therapy and cesarean section.¹ In LQTS the postpartum period is associated with increased arrhythmic event risk, especially in LQT2.²

Beta-blockers can be given with caution during pregnancy, but the risks should be carefully reviewed with the patient and her other doctors. In addition genetic counseling regarding the (usually) autosomal dominant mode of inheritance should be discussed in advance of pregnancy if possible. Most cases of CPVT appear to be due to mutations in the cardiac ryanodine receptor (RyR2), but rarely an autosomal recessive pattern can be caused by mutations in calsequestrin 2 (CASQ2).

Genetic testing revealed no known mutations consistent with Long QT or Catecholaminergic Polymorphic Ventricular Tachycardia. An ICD was implanted and she has done well on beta-blockers. She has been advised against competitive running. Though she continues to have episodes of ventricular tachycardia, she has not required ICD therapy. Due to consideration for pregnancy, she did undergo genetic testing and her beta-blocker was switched from atenolol to propranolol. She is now in her second trimester of pregnancy and is doing well without any cardiac or arrhythmic events.

Editorial Comment

This case serves to illustrate the importance of careful history in a patient with syncope. Even though she has had a history of prior syncope consistent with vasovagal etiologies in the past, the new episode involves details that are worrisome. Syncope occurring during exercise always warrants a thorough evaluation. Furthermore, the frequent polymorphic ectopy (many in pairs) and nonsustained ventricular tachycardia during exercise and recovery are consistent with a high-risk clinical status in this patient.

Genotype-phenotype correlations for hereditary arrhythmias can be useful for confirmation of clinical diagnoses and aid in more targeted management recommendations such as avoiding exercise and competitive sports with Long QT Syndrome 1 or alarm clocks/startling arousals with Long QT Syndrome 2. Furthermore, if genetic testing de-

fects a known mutation, the risks in children of affected parents can be assessed or even ruled out with known hereditary transmittance patterns. However, not all affected patients will test positive for known mutations. Of patients with CPVT, it is estimated that 50–70% are associated with a known disease-causing mutation (as compared with 70% for LQTS). In this regard it is important to stress the fact that traditional genetic testing may be limited in detecting unconventional mutations such as large deletion/duplication rearrangements in LQTS and possibly CPVT patients.^{3,4} Thus, more thorough genetic testing may be warranted in this high-risk patient.

For patients with no identifiable mutations, management and treatment should still be based on their phenotypic presentation consistent with the clinical evaluation. In this case, a singular diagnosis is not easily arrived at. Despite the lack of a positive genetic test in this patient, the clinical presentation of the patient and the ETT findings are consistent with a primary diagnosis of CPVT, although LQTS could be a reasonable alternative diagnosis in view of the abnormal repolarization seen on the ECG tracing at presentation. These diagnoses under consideration warrant the use beta-blocker therapy as a first-line therapeutic measure. However, the malignant ventricular arrhythmia findings during exercise and recovery suggest that follow-up and consideration of an ICD are warranted if a patient is deemed to be at high risk or if symptoms occur during medical therapy.

REFERENCES

1. Walker NL, Cobbe SM, McGavigan AD. Paroxysmal bidirectional ventricular tachycardia with tachycardiomyopathy in a pregnant woman. *Acta Cardiol* 2009;64:419–422.
2. Seth R, Moss AJ, McNitt S, et al. Long QT syndrome and pregnancy. *J Am Col Cardiol* 2007;49:1092–1098.
3. Tester DJ, Benton AJ, Train L, et al. Prevalence and spectrum of large deletions or duplications in the major long QT syndrome-susceptibility genes and implications for long QT syndrome genetic testing. *Am J Cardiol* 2010;106:1124–1128.
4. Eddy CA, MacCormick JM, Chung SK, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. *Heart Rhythm* 2008;5:1275–1281.